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PANEL DISCUSSION ON OSTEOPOROSIS*

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Panelists: DANIEL LASZLO, M.D.,‡ NATHAN W. SHOCK, PH.D.,§
AND G. DONALD WHEDON, M.D.‖

MODERATOR EPHRAIM SHORR: This panel discussion deals with osteoporosis, a subject that has always been of great concern to those of us working with patients in the older age group, and that should be and will be of increasing concern as we become aware of the frequency with which osteoporosis complicates the well-being of older people in our population.

The panel members propose to discuss osteoporosis in such a manner as to stimulate questions that will reveal whatever doubts may exist in your minds as to the concepts that we are exploring.

Dr. Laszlo will open the discussion.

DR. DANIEL LASZLO[1]: Osteoporosis is not a rare condition. Because it is relatively asymptomatic, most of the cases remain undiagnosed.

In a recent survey, Dr. Anderson in England compiled a review of approximately 280 cases of osteoporosis reported within the last ten years. It is interesting that the incidence among females was much higher than among males. Nearly 80 per cent of all the cases reported occurred in females. This raises the question as to etiology and nomenclature—Shall we call it senile osteoporosis, or shall we call it postmenopausal osteoporosis because of its prevalence in females?

I shall discuss some of the difficulties encountered in diagnosis. The disease

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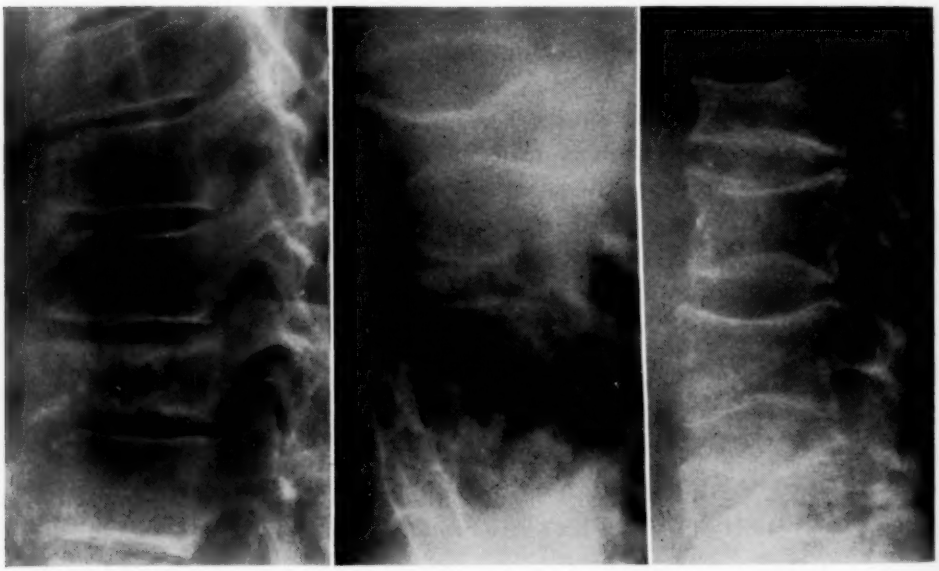
occurs in older people. As the complaints are few, the diagnosis is usually made only when the "disease" is advanced and the pain sufficient to make the patient seek medical advice. One wonders how to diagnose osteoporosis at an early stage and what help laboratory aids can provide in reaching this goal.

The routine chemical determinations available today are of meager help. The serum levels of calcium, phosphorus and alkaline phosphatase are usually within the normal range, in contrast to findings in other metabolic or neoplastic bone disease in which these are of considerable diagnostic importance. Even the measurement of 24-hour urinary calcium and of calcium balance on a low-calcium diet are of little help. They may be well within normal limits. In advanced cases of osteoporosis, the urinary calcium may even be distinctly low.

Figure 1A shows the vertebrae of an 82-year-old woman who had ascites, left pleural effusion, and a large firm abdominal mass. She was thought to have metastases to the spine. However, she actually had a large benign fibroma of the ovary and osteoporosis. Figure 1B shows the vertebrae of a man who was thought to have generalized carcinomatosis secondary to carcinoma of the lung; instead, he had emphysema, bronchitis, atelectasis, and osteoporosis. Conversely, Figure 1C shows the vertebrae of a patient with multiple myeloma, in whom the previous diagnosis had been osteoporosis.

The importance of early diagnosis of osteoporosis and of differential diagnosis



A B C

FIG. 1. **A.** Vertebrae of 82-year-old woman with osteoporosis and Meig's syndrome. The previous diagnosis had been peritoneal carcinomatosis with metastases to the spine. **B.** Vertebrae of a 64-year-old man with osteoporosis, emphysema and atelectasis. The previous diagnosis had been carcinoma of the lung with metastases to the spine. **C.** Vertebrae of man aged 60 with multiple myeloma. The previous diagnosis had been osteoporosis. (From Spencer, H.; Hausinger, A., and Laszlo, D.: The calcium tolerance test in senile osteoporosis, *J. Am. Geriatrics Soc.* **2:** 19, 1954.)

of this condition from primary or secondary malignancy of the bone need not be stressed. Errors in these difficult differential diagnoses unfortunately are not uncommon.

When evidence of marked mineral loss is seen on roentgenograms and in histologic sections, one wonders how many years it took for all these changes to occur. What are the etiologic factors?

Is osteoporosis due to malnutrition? It is known that older people may suffer from anorexia and, in addition, may acquire certain food habits that result in insufficient calcium, protein and vitamin intake.

Osteoporosis occurs at an age when the gastro-intestinal tract functions less efficiently. Achlorhydria is rather frequent in elderly people. Therefore, the problem arises whether this decreased efficiency of the gastro-intestinal tract contributes in part to the development of osteoporosis. Could it be that *decreased intestinal absorption* of calcium and of other nutrients, vital for the maintenance of skeletal integrity, is a contributory factor?

Is impairment of smaller blood vessels and capillaries in the aged person preventing the proper transport of nutrients to the skeleton? Do physiochemical changes occur in the cell membranes that interfere with the proper exchange of nutrients and fluids from the environment into the cells in senescence?

What role is played by decreased physical activity and immobilization?

Finally, is the decline of hormonal activity the cause of osteoporosis?

A few of the problems outlined are under active investigation in our laboratories. This investigation has been facilitated by the development of newer technics which I shall mention briefly. My remarks will be confined to two problems. The first deals with the responses of patients with osteoporosis to a standard dose of calcium administered intravenously and the effects of hormonal therapy thereon. This problem was investigated with the aid of the *calcium tolerance test*. The second question is whether the absorption of dietary calcium is impaired in patients with osteoporosis. This problem was investigated by *metabolic balance technics* and by the use of tracer doses of *radiocalcium*.

The calcium tolerance test is performed in the following manner: A standard 50-ml. dose of calcium gluconate is infused slowly over a period of four hours in fasting patients. The urinary calcium is determined on the day before, on the day of calcium infusion, and on the day thereafter. The patients are maintained on a low-calcium diet for several days prior to, and during the test. Excess calcium excretion occurs on the day of infusion as compared with the days before and after. This excess is expressed as a percentage of the administered dose. The remainder is the percentage of the dose that is retained, and that seems to reflect the bone metabolism of the patients.

In Figure 2, the average values obtained in 56 calcium tolerance tests (Lewin and Spencer (1a), and Laszlo and Spencer (1b)) are arranged in three groups: in Group B were patients with "normal" mineral metabolism. The average 24-hour urinary calcium excretion in this group was 71 mg. It rose to 200 mg. on the test day, and returned to 79 mg. the subsequent day. The excess calcium excretion was approximately 130 mg., or 29 per cent of the administered calcium. The cal-

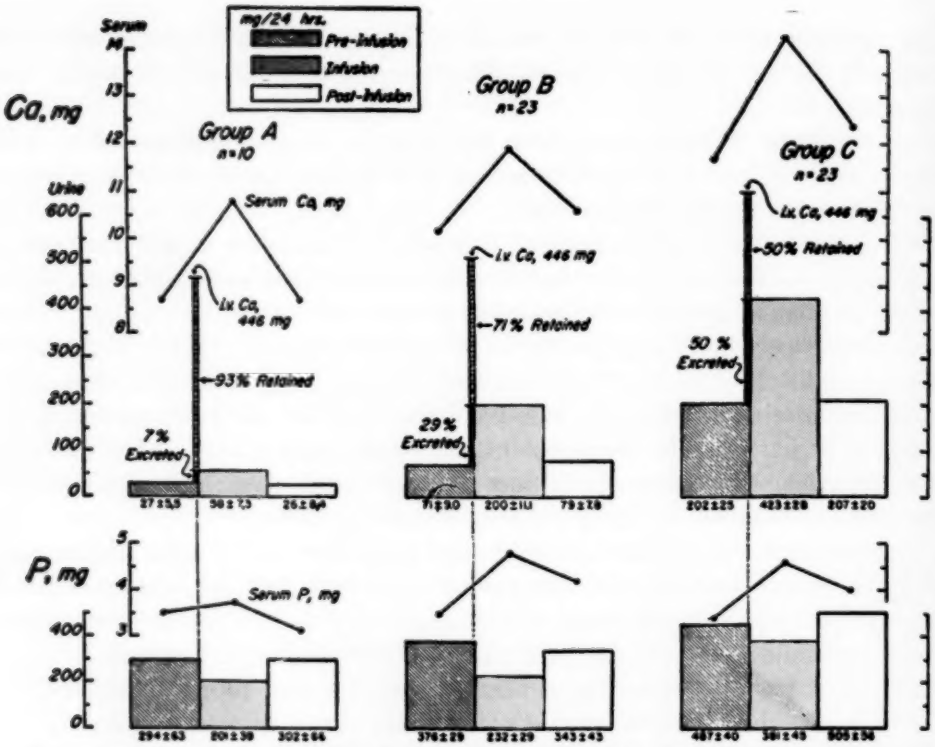


FIG. 2. Results of the calcium tolerance test performed in 56 patients. Group A: patients with increased calcium retention. Group B: patients with normal mineral metabolism. Group C: patients with decreased calcium retention.

(The editors of this journal wish to express their appreciation to Earl Engle, M.D., and Gregory Pincus, M.D., editors, for their kind permission to reprint this figure, which first appeared in the chapter on "Newer Technics in the Study of Calcium Metabolism in Man and Effects of Hormones Thereon," in *Hormones and the Aging Process*, New York, Academic Press Inc., 1956.)

cium retention was 71 per cent. In Group C are the average values for calcium tolerance tests performed on patients who had an elevated urinary calcium before the test. On the test day, the urinary calcium excretion rose to higher values than in the normal group, the average being 423 mg. in twenty-four hours. Only 50 per cent of the infused calcium was retained. In Group A are the average values for calcium tolerance tests in patients with increased calcium retention. The urinary calcium excretion was 27 mg. prior to the infusion. It rose to only 58 mg. in twenty-four hours on the test day, with 93 per cent of the infused dose being retained and only 7 per cent excreted.

Abnormal mineral metabolism in metabolic bone diseases or in tumors affecting the skeleton is best reflected by changes in the urinary calcium excretion rather than by fecal calcium losses. The urinary calcium excretion is regulated in several ways, principally by the parathyroid gland, and depends in part on the opposing forces of calcium deposition and release in the bone matrix. For instance, it may be assumed theoretically that an increased calcium excretion may result from either of two types of disturbed equilibrium between acceptance and release of

TABLE 1

Schematic Presentation of Factors Influencing Spontaneous and Induced Calcinuria

Calcium Balance	Calcinuria (mg./24 hr.)			Retention of Infused Calcium (446 mg.)	
	Spontaneous	Induced*	Excess	mg.	Utilization %
Normal	70 (−170 + 100)†	200	130	316	71
Demineralization					
Patient A	170 (−270 + 100)	300	130	316	71
Patient B	170 (−170 + 0)	400	230	216	49

* Calcinuria on the day of the test.

† Figures in parentheses represent the amount of calcium assumed to be released by osteoclastic activity (negative values) and re-utilized for bone formation (positive values). The difference of the two is assumed to represent spontaneous calcinuria.

(From Spencer, H.; Hausinger, A., and Laszlo, D.: The calcium tolerance test in senile osteoporosis, *J. Am. Geriatrics Soc.* **2:** 19, 1954.)

minerals—increased release with normal acceptance, or normal release and decreased acceptance. An attempt has been made to analyze the underlying mechanism of increased urinary calcium excretion with the aid of the calcium tolerance test. A schematic presentation of factors influencing the spontaneous and induced calciuria is shown in Table 1.

On the basis of experimental data currently available, it is assumed that patients with senile or postmenopausal osteoporosis have a defect in the acceptance of intravenously administered calcium similar to that illustrated in the schematic presentation for Patient B in Table 1 (Spencer, Hausinger, and Laszlo).

The calcium tolerance test performed on a patient with Cushing's disease due to an adrenal adenoma is shown in Figure 3. Preoperatively, the urinary calcium excretion was 200 mg. in twenty-four hours. On the test day, it rose to an abnormally high value. Therefore, considerably less than the normal fraction of the test dose was retained by this patient. Following the removal of the adrenal adenoma, a marked change in the calcium metabolism occurred as reflected by the results of the calcium tolerance test: the urinary calcium excretion decreased considerably and approximately 80 per cent of the test dose was retained when the patient was retested (Spencer, Lewin, and Laszlo (2 and 1b)).

Figure 4 shows the pattern of calcium excretion following the calcium tolerance test in senile or postmenopausal osteoporosis and the effect of hormonal medication. The retention of the intravenous dose in the first and in the third test was abnormally low. Retention was nearly normal in the second test, which was performed while the patient was under hormonal medication. Increased excretion of calcium on the days of the calcium tolerance tests performed prior to, and after discontinuation of hormonal medication was the only chemical indication of disturbed calcium metabolism. Serum calcium and phosphorus levels, urinary calcium and phosphorus excretions, and the metabolic balances of nitrogen, calcium and phosphorus were well within the normal range.

I should like to spend a few minutes discussing whether impairment of ab-

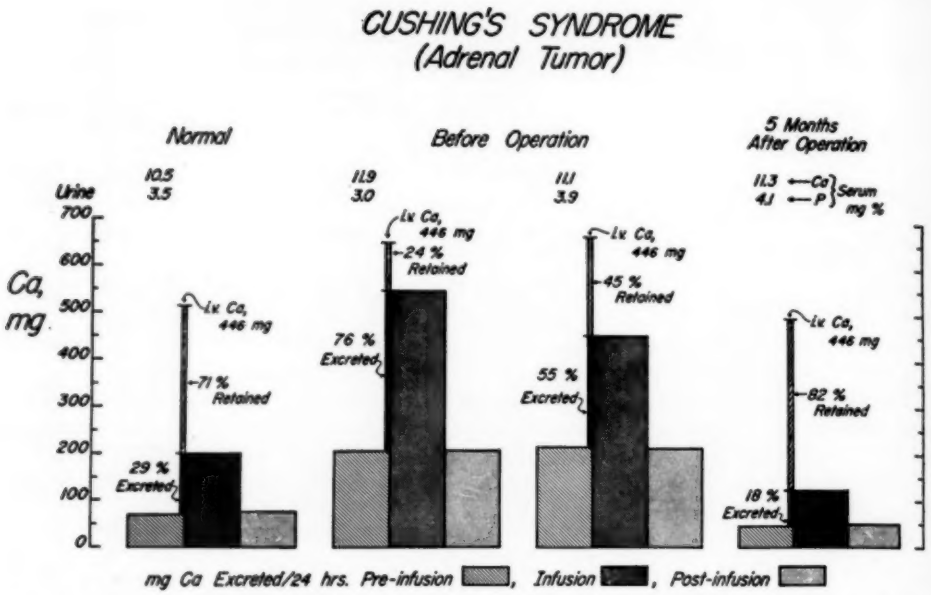


FIG. 3. Results of calcium tolerance test in a case of Cushing's syndrome, before and after removal of an adrenal adenoma.

sorption of food constituents, such as dietary calcium, may play a role in the development of senile osteoporosis, and whether therapeutic measures used in the treatment of this condition can be shown to affect the absorption of calcium.

The absorption of dietary calcium can be measured by metabolic balance technics. This involves the determination of calcium balances during varying intake levels of dietary calcium, and relating the improvements in calcium balance to the differences in calcium intake, according to the formula:

$$\text{Per cent utilization of dietary calcium} = \frac{\text{Improvement in calcium balance}}{\text{Difference in calcium intake}} \times 100$$

In young persons, the utilization of dietary calcium is high—up to 70 per cent. In a review of data obtained from the literature and also our own, the impression is gained that the absorption of dietary calcium (as measured by this technic) is much lower in patients with osteoporosis than in patients of similar age groups without osteoporosis. As little as 8 per cent of the added calcium was utilized by some of these patients.

A new technic has recently been developed that permits the measurement of absorption of dietary calcium at *one* calcium intake level by the use of radiocalcium as the tracer. By this tracer technic, the fecal calcium can be separated into endogenous and exogenous calcium fractions. The former is contributed by the digestive juices secreted into the intestinal canal, the latter is the dietary calcium that passes unabsorbed. The study is performed in the following manner: the patient receives a small dose (less than 0.5 μc. of Ca^{45} per kilogram of body weight) orally together with breakfast. The plasma levels and urinary and fecal

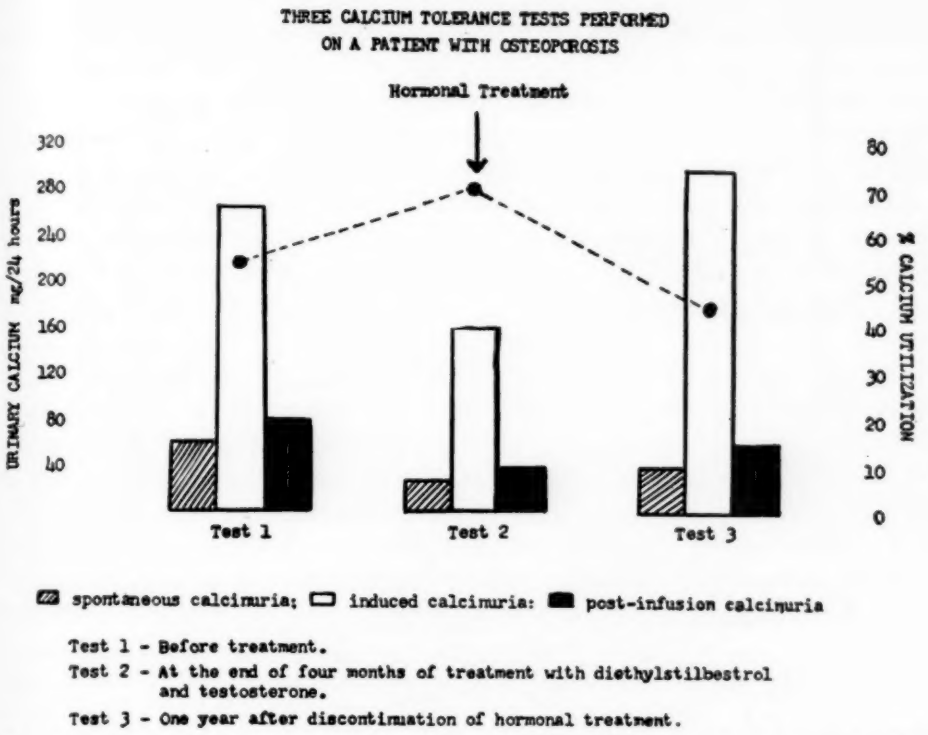


FIG. 4. Effect of hormonal therapy on urinary calcium in a case of osteoporosis. (From Spencer, H.; Hausinger, A., and Laszlo, D.: The calcium tolerance test in senile osteoporosis, *J. Am. Geriatrics Soc.* **2:** 19, 1954.)

excretions are analyzed daily for calcium and radiocalcium. The tracer uniformly labels all the calcium of the body fluids so that the specific activity of calcium, *i.e.*, the ratio of radioactive to stable calcium, is the same in the plasma and in the fluids (digestive juices and urine) derived from it. However, the specific activity of the fecal calcium is lower due to the presence of stable calcium derived from the food that passed unabsorbed. This lowering of the fecal specific activity is therefore a direct measure of the amount of calcium in the stool which is of dietary origin. Knowing the calcium intake and the dietary calcium losses in the stool, the utilization of dietary calcium can be determined. Figure 5 illustrates a study in which this technic was employed (Blau, Spencer, Swernov and Laszlo: *Science* **120:** 1029, 1954).

Senile or postmenopausal osteoporosis is a condition that occurs frequently and usually remains undiagnosed until it is far advanced. As it is prevalent in the older age group, it is not infrequently diagnosed as metastatic carcinoma. The importance of the early diagnosis of osteoporosis and of differentiating it from metastatic carcinoma and multiple myeloma cannot be overemphasized. The chemical aids so helpful in a variety of conditions affecting the skeletal system—determination of serum calcium and phosphorus levels, urinary calcium,

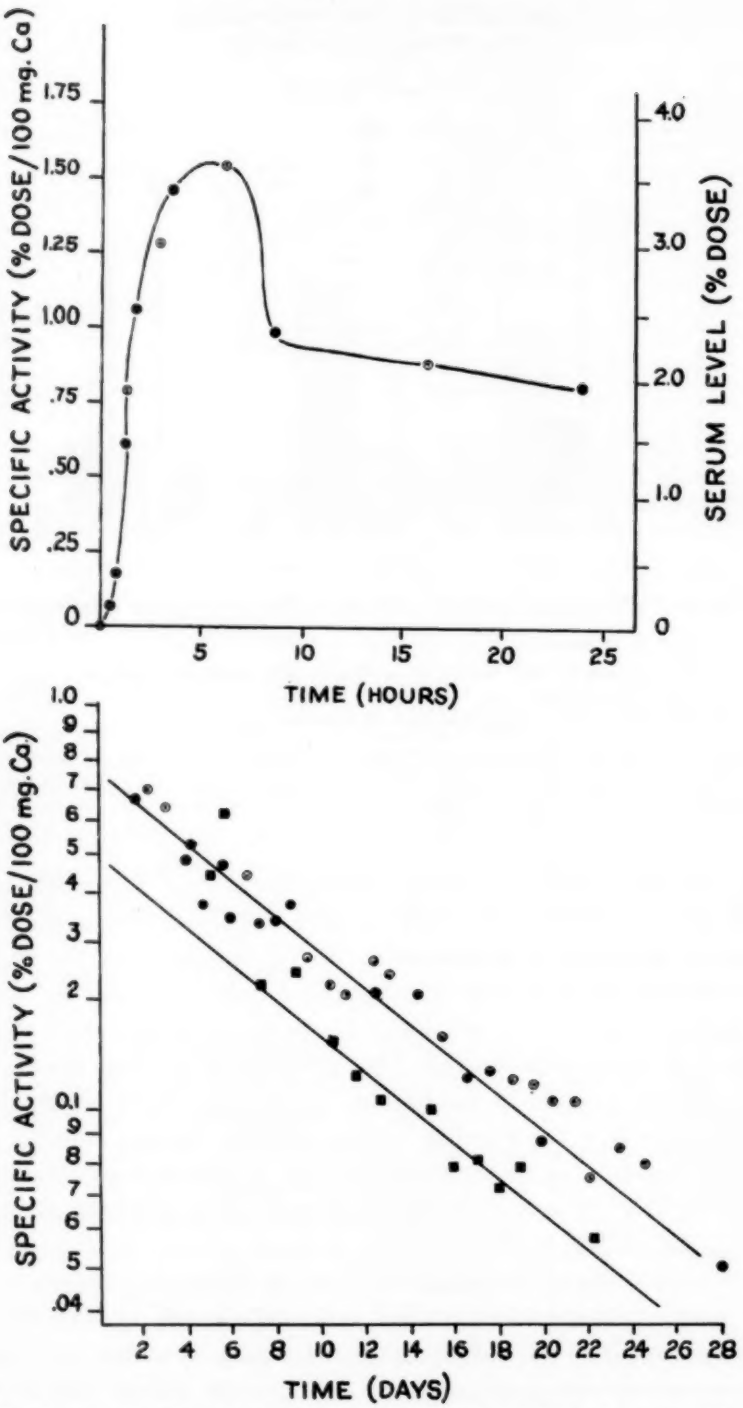


FIG. 5. Calcium and Ca^{45} content of serum, urine and stool of a human subject. Symbols: ● plasma, ⊙ urine, ■ stool. (From Blau, M.; Spencer, H.; Swernov, J., and Laszlo, D.: Utilization and intestinal excretion of calcium in man, *Science* **120:** 1029, 1954.)

and calcium balances—are of little diagnostic aid in osteoporosis. The length of time required for the development of this condition is not known. The underlying mechanism is not clear. Some of the factors that may contribute to its development have been enumerated, and two of the technics employed in this laboratory for the study of senile osteoporosis (the calcium tolerance test and the radiocalcium technic) have been discussed. It appears that the acceptance of intravenously administered calcium is impaired in certain cases of osteoporosis and that it improves following hormonal therapy. It also appears that patients with osteoporosis absorb calcium from the intestinal tract less efficiently than normal persons.

MODERATOR SHORR: Dr. Laszlo has told us that the conventional methods of investigating mineral metabolism by the analysis of urinary excretion do not seem to be helpful in distinguishing patients with osteoporosis from those without, and that we undoubtedly must resort to more sophisticated technics.

The calcium tolerance test as a measure of the capacity to retain a given load of calcium promises to be of considerable help when the differentiation cannot be made with certainty on roentgenographic grounds. Even under those circumstances, it may be of help in differentiating the conditions that lead to bone rarefaction.

Are there some questions that the audience would like to ask Dr. Laszlo?

There seems to be general agreement.

DR. HENRY JAFFE: I should like to ask Dr. Laszlo a question.

There is no doubt that hormonal therapy does improve these patients in the postmenopausal state. Can you explain why significant roentgenographic evidence of improvement is not seen?

DR. LASZLO: I am not sure that I can explain it so that it will be acceptable to all. It seems that, as Dr. Shorr has pointed out, a great deal of mineral must be deposited in or lost from bone for the change to be evident on roentgenograms. It may be assumed that the technic of roentgenographic study of the skeleton is not sufficiently sensitive to pick up these early changes.

MODERATOR SHORR: Mention was made earlier in the discussion of how the habits of patients in the older age group might modify the ability of the skeleton to take advantage of the stresses and strains that normally are helpful in the constant rebuilding of the skeleton during life. One of these changes was the relative immobility of those in the older age group. In addition, various circumstances that might be called episodes or accidents occur in these elderly people.

Dr. Whedon has devoted a great deal of time to the consideration of this particular factor. I should like to call upon him for his experience with respect to this phase of the life process in the older age group.

DR. G. DONALD WHEDON: The possible evil effects of immobilization or of recumbency of long duration have been cited frequently in recent years. Some of those mentioned have been phlebothrombosis, thrombophlebitis, hypostatic pneumonia, constipation, urinary retention, and decubitus ulcers. These are familiar terms to physicians dealing with the elderly.

Today I wish to present some data dealing with the effects of immobilization

on calcium metabolism. They indicate that the immobilized patient becomes clearly predisposed to the development of osteoporosis, and that incidental to the loss of minerals from the skeleton and their excretion, he also becomes predisposed to the development of calculi in the urinary tract.

These matters are of real significance to the physician charged with the management of a patient with a fracture of the hip or spine, a paraplegic patient, or one otherwise invalided for many weeks or months.

First, I shall review some published studies on the effects of immobilization or recumbency on the metabolism of normal individuals (3). In an effort to dissociate the metabolic effects of immobilization *per se* from the combination of effects in any disease of which confinement to bed is a part, 4 healthy young men were placed in plaster casts from waist to toes for six to seven weeks.

Metabolic balance studies were conducted during the phase of immobilization and for several weeks before and after. The dietary intakes were kept constant throughout the period of observation. The principal effects noted were a modest increase in nitrogen excretion, a loss of the reflexes that ensure adequate circulation in the upright position, and a distinct loss of calcium and phosphorus (Fig. 6).

The increase in urinary calcium, although variable in absolute amount from subject to subject, was more than twofold in each subject. There was an accompanying lack of compensatory increase in urinary citric acid, and a slight

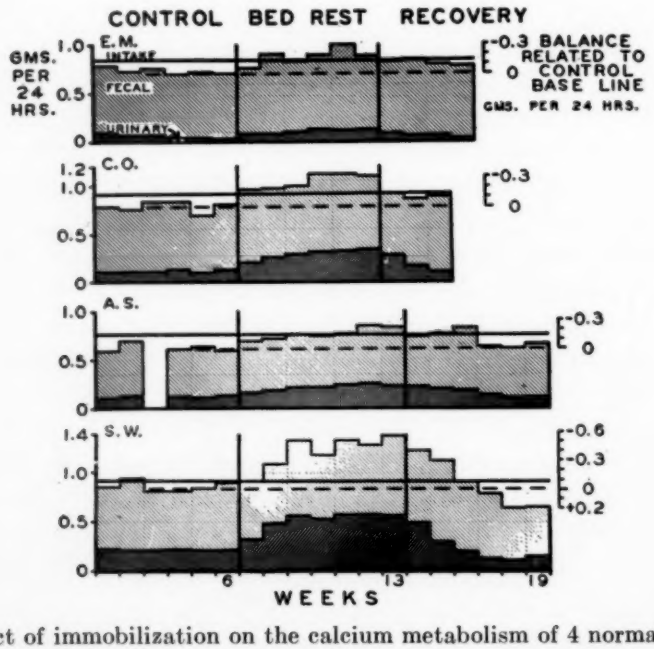


FIG. 6. Effect of immobilization on the calcium metabolism of 4 normal male subjects. In each, the daily calcium intake was kept constant throughout all periods of the experiment. For each subject the control baseline (interrupted horizontal line) is an average of the total outputs of the last four control weeks.

(The editors of this journal wish to express their appreciation to W. B. Saunders Company for permission to reprint this figure from Whedon, G. D.: Management of the effects of recumbency, *Med. Clin. North America* **35:** 545 (March) 1951.)

shift of urinary pH towards alkalinity, both factors having the effect of decreasing the solubility of calcium in the urine.

These findings indicated a metabolic basis for the relatively high incidence of calcium-phosphate calculi in the urinary tract in immobilizing diseases.

The magnitude of the loss of calcium which occurred in these immobilized normal individuals should be emphasized. The average peak urinary calcium excretion in these subjects was 340 mg. per day, which was approximately two-thirds of the average peak urinary calcium excretion in a comparable group of young males with fractures who were studied by Howard, Parson and Bigham (4).

Both the urinary calcium excretion data and the total balance data indicated that during immobilization, calcium excretion increased gradually and reached a plateau at the fourth to fifth week after the application of the casts. There was no indication of any subsidence of the rate of calcium loss at the time immobilization was discontinued.

The total amounts of calcium lost during the six to seven weeks of immobilization (9 to 24 Gm.) amounted to between 1 and 2 per cent of the estimated total skeletal calcium. There was no roentgenographic evidence of mineral loss from the bones.

This percentage of loss does not seem great in terms of commonly accepted estimates of the amounts of the total body calcium that must be lost before demineralization becomes demonstrable roentgenographically. However, such estimates (varying from 10 to 30 per cent) may be somewhat too high, at least for the immobilization type of osteoporosis.

The effects of immobilization on calcium metabolism may seem even more striking when we examine the data on calcium loss in a severely immobilizing disease such as poliomyelitis. Metabolic observations have been carried out on a group of 9 patients with extensive paralysis due to acute anterior poliomyelitis (5).

The age range of the patients was from 17 to 39 years. Seven were studied during the acute and early convalescent phases of the disease, so that the developing picture of disordered calcium metabolism was outlined almost from its onset. Twenty-four-hour urine collections were begun within the first week of illness in 4 of these 7 patients. Constant dietary intakes were instituted within the first few weeks.

The urinary calcium climbed gradually and became greatest at the fifth week after the onset of the illness. The maximal urinary calcium for a six-day metabolic period ranged from 381 to 789 mg. per day, the mean being 572 mg. per day. The urinary calcium remained above 250 mg. per day for an average of five and a half months.

The maximal negative calcium balances averaged 540 mg. per day. They were noted, on the average, nine weeks after the onset of the illness. The negative calcium balance continued for an average of seven months.

In view of the lack of specific data on the percentage of total body calcium that must be lost before osteoporosis becomes evident, the measured calcium losses of these patients were analyzed in relation to roentgenographic findings.

The initial evidence of porosis was usually a patchy demineralization and increase in trabecular marking in the lower extremities near the joints, most often in the necks or distal ends of the femur. In 3 patients, the first abnormality noted was a submetaphyseal band of rarefaction in the distal tibiae.

These early roentgenographic signs of demineralization appeared on the average three months after onset of the paralysis, and occurred with an average loss of 1.9 per cent of the total body calcium. The estimated total body calcium was taken as 2 per cent of the pre-illness weight. As recumbency continued, the areas mentioned became more radiolucent, and changes appeared in the rami of the pubis and ischium, and in the acetabular fossa of the innominate bone. The total calcium losses averaged 4 per cent, with a range of 1 to 8.5 per cent. These losses were not associated with any detectable roentgenographic changes in the spine. Definite demineralization of the spine was noted, however, in 4 other patients who were not undergoing metabolic study. These latter patients had extreme paralysis, and had been immobilized for many months before they were examined roentgenographically.

Hence, the site of the involvement of osteoporosis associated with disuse or immobilization is different from that of postmenopausal or senile osteoporosis. The latter appears to involve first and principally the spine, then the pelvis, and then the ribs. Osteoporosis in immobilized patients occurs in the following preferred sites: the distal ends of the bones of the lower extremities, the necks of the femurs, and then the pelvis. Because of this specific localization, the first roentgenographic evidence of demineralization may be detected at a time when there has been a relatively modest total calcium loss (2 per cent). Severe immobilization ultimately leads to osteoporosis of the spine as seen roentgenographically, but evidently not until after 10 per cent or more of the total body calcium has been lost.

These data on the relation between calcium loss and the development of demonstrable osteoporosis in immobilization obviously cannot be used to estimate the quantitative loss of calcium from the spine in postmenopausal or senile osteoporosis.

In the individual patient with postmenopausal or senile osteoporosis, it is possible that recumbency or even reduced activity may contribute to some extent to mineral loss. The roentgenograms of the patient may reveal demineralization of the postmenopausal or senile type in the spine, and demineralization of the immobilization type elsewhere, particularly in the pelvis and lower extremities.

The principal therapeutic measure that should be applied in the management of elderly patients confined to bed with some immobilizing condition is evident. After the patient has had three to four weeks of bed rest, every effort should be expended toward getting him out of bed and back on his feet.

Urinary calcium reaches maximal levels at the fifth or sixth week, so that the threat of calculi formation begins to assume importance at about that time. If postmenopausal or senile osteoporosis is already present, the demineralization will begin to be significantly increased by immobilization approximately six weeks after the beginning of the immobilization.

MODERATOR SHORR: Thank you.

As I listened to Dr. Whedon I got the impression, fortified by objective evidence, that immobilization *per se* can make a major contribution to the demineralization of the skeleton if it is sufficiently prolonged and sufficiently marked. I also gathered that the pronounced losses that occurred in the polio patients and in the normal male subjects are extreme examples of what may be taking place in patients in the older age group confined to bed as a result of concurrent illness. Thus, it is often necessary to study conditions in which the degree of the immobilization is profound, for only when it is intense and exaggerated can we become aware of the effects, which may be less easy to measure quantitatively in the elderly patient who is forced to remain in bed.

The measures of rapid mobilization that are suggested are sometimes not possible to achieve. Dr. Whedon, would you like to speak briefly about other measures that can be instituted when the patient cannot be up and about as soon as you would suggest?

DR. WHEDON: First, I shall insert a brief statement about measures to be taken with respect to fluid and calcium intake for the patient who has to remain in bed. Bearing in mind the threat of calculus formation, it is obvious that attention should be given to maintaining an adequate urinary output and volume by providing an adequate fluid intake.

In addition, our belief at present is that one should not force calcium upon such a patient in the hope that raising the calcium intake may diminish the severity of the expected demineralization of the skeleton. Although increasing the calcium intake may have some beneficial effect on the over-all calcium balance, there is the possibility that some of the increased calcium absorbed will lead to an increase in the urinary secretion of calcium, thus enhancing the likelihood of calculus formation.

One therapeutic measure that has been suggested recently for the management of the patient who must be immobilized for a considerable period of time is the use of the slowly oscillating (Sanders) bed. This bed has not been fully evaluated but thus far the metabolic studies conducted with it in patients with various diseases have not revealed a favorable influence on calcium, nitrogen or phosphorus metabolism.

The thought that this slowly oscillating bed might be of value for the invalided patient stems from an experiment carried out with normal subjects (6). During immobilization on such a bed, the loss of minerals was approximately half of what it had been in the original experiment in which the subjects were immobilized on a regular, fixed hospital bed.

The oscillating bed has since been used for brief studies in severely paralyzed poliomyelitis patients. During the past year, its use has been reported in a group of 5 patients with paraplegia (7). In neither of these experiments was there a clearly demonstrable ameliorating influence on calcium metabolism. In both types of paralysis, however, there is a lack of normal muscle power and, therefore, of the usual expected stress and strain upon the skeleton.

In all of the studies with this bed, a considerable improvement occurred in

vascular tone and in the reflexes concerned with good circulation in the upright position.

MODERATOR SHORR: A statement was made by Dr. Laszlo regarding the suspected impairment of absorption of lime salts and other nutrients in the older age group. This is an area in which Dr. Shock has done a great deal of work.

Will you tell us, Dr. Shock, about your work on the relation of nutritional measures to osteoporosis in elderly patients?

DR. NATHAN W. SHOCK: I feel a bit embarrassed at participating in a symposium dealing with a disease process, but I presume that the intent is for me to offer some of the physiologic background, particularly the physiologic characteristics of older people free from disease as contrasted with the patients that have been discussed.

The basis for my discussion stems from studies carried out in our laboratories, in collaboration with Dr. Morton Bogdonoff and Dr. Donald Watkin, utilizing the metabolic balance technic (8, 9).

First of all, I can say categorically that we have investigated several nutrients and as yet have found no evidence of impairment in the absorption of any of these materials in older people.

Our studies have all been made on older persons who were carefully selected, in that they were free from all of the laboratory and clinical signs and symptoms of osteoporosis that have been described. This does not mean that they did not have osteoporosis, but at least it could not be identified. They were all ambulatory, so that the effects of inactivity on nitrogen and calcium balances discussed by Dr. Whedon would not apply. Most of the patients studied were actually working about the grounds and on the wards of the Baltimore City Hospitals.

For our studies on the retention of calcium, we chose diets that would ensure a positive nitrogen balance throughout the duration of the studies. Consequently, the patients were fed a rather rich diet. The protein intake was relatively high, amounting to 90 or 100 Gm. a day. This is more protein than persons in the 70–80 year old category really care to consume, so that our problem was partly one of maintaining this high intake. The diet was relatively high in terms of caloric levels, supplying 2,500 to 2,600 calories per day. This was supplemented by 15,000 international units of vitamin A and 1,500 international units of vitamin D per day.

With such a diet as a background, we varied the calcium intake from the level of 107 mg. per day up to 1,500 mg. per day in each person tested. The problem under investigation was whether or not the human being behaves like the rat. In the studies reported by Dr. Clive McCay and his colleagues, when rats were given a suboptimal diet, the old ones lost calcium from the body at a more rapid rate than did the young ones; thus they required a high calcium intake in order to maintain balance. The old rats were much more sensitive to calcium loss induced by increasing the fat content of the diet than were the younger animals.

Seven men aged 66 to 83 years were tested during four to six levels of calcium

intake (107 to 1,500 mg. per day). From these observations, we were able to estimate the theoretical amount of calcium required to maintain balance.

In our experience, the values were not significantly different from those reported for younger individuals. When receiving diets containing 107 to 138 mg. of calcium per day for a period of approximately six weeks, all of our subjects had a rather marked negative calcium balance, losing as much as 300 mg. of calcium per day. Increasing the daily calcium intake stepwise, we found a borderline zone at a level of 600 to 800 mg. of calcium, where subjects attained equilibrium. All of our subjects were able to retain calcium when the intake was raised to 1,200 or 1,500 mg. per day. Positive balances of 100 to 200 mg. per day were found in all when the calcium intake was raised to 1,500 mg. per day.

In addition to the normal men, we also studied 3 men aged 68 to 83 years, who suffered from osteoporosis. We found that the osteoporotic subjects had a negative calcium balance at an intake level of 600 to 800 mg. of calcium per day, even though the nitrogen balance was positive. However, each man was able to retain some calcium when the intake was increased, though not as much as in the case of the nonosteoporotic group. A marked increase in calcium retention occurred at intake levels of 600 to 700 mg. calcium per day when stilbestrol (6 mg. per day) was administered orally.

In all of these studies we followed both the urinary and the fecal excretion. When the calcium intake was increased, although there were wide individual differences, the urinary calcium increased, indicating that at least part of the administered calcium was being absorbed.

Our metabolic balance technic does not permit a precise statement of the percentage of ingested calcium that is retained. Additional studies ought to be made in elderly people without osteoporosis, using the technics described by Dr. Laszlo, that is, the calcium tolerance test as well as the absorption values derived from the use of radioactive isotopes.

Thus far, we have been unable to find age differences in absorption. This does not mean that there are no differences. All I can say is that, by the technics that we have applied, we have been unable to demonstrate significant age differences in the absorption of protein, calcium, glucose, or even vitamin A.

MODERATOR SHORR: Do I interpret your findings aright if I say that, in reference to the use of normal nutritional dietary components, you are optimistic that an adequate daily diet containing 800 to 1,200 mg. of calcium, 85 Gm. of protein, and fat to supply about 2,000 calories, should keep an elderly person in mineral equilibrium?

DR. SHOCK: That has been our experience. Many elderly people in our population may not be receiving anything like that kind of diet, either for reasons of habit over a lifetime of eating, or because of the sheer economics of being unable to purchase protein in that quantity with the funds they have available.

MODERATOR SHORR: If we take your standard as something at which to aim, then it is up to the individual physician to exercise ingenuity in seeing that these optimal quantities are fed to the patient in such a manner as to be acceptable and actually to be taken.

The problem in the older age group, as I recall from conversations with you about these patients in your own hospital, was that they were supposed to have a reasonably adequate diet in the hospital wards, and it was their failure to accept it that was so striking in your studies carried out while they were receiving a diet which they could take. Is that correct?

DR. SHOCK: Yes.

MODERATOR SHORR: Then this is our problem: We have the standards that will, if met, maintain elderly patients in equilibrium; it is difficult to get them to take the necessary diet; therefore, it is a challenge to the physician to see that the standards are met.

I should like to discuss some other therapeutic measures that should be considered in the management of this problem.

Table 2 shows that in dealing with the skeleton there is a considerable body of protoplasm to replenish and repair. In the skeleton of an average 70-Kg. man, there is about 1.5 Kg. of calcium, about 0.5 Kg. of phosphorus, a not inconsiderable quantity of nitrogen, and 1.7 Kg. of protein. It is the magnitude of this repair in osteoporosis that often may account for the failure of roentgenograms to show increased density.

Various measures have proved helpful. Lime salts added to the diet, for example, are well absorbed in many instances. We believe that if it is difficult to get as much as 1.5 Gm. of calcium in dietary constituents, one should resort to the use of added lime—added calcium, in the form of calcium lactate for example.

An agent which is a stepbrother to calcium—strontium—has been the subject of our attention for several years. There is some evidence that this substance, which behaves just like calcium with respect to its ability to make good bone provided it is fed along with calcium, may often be retained in better fashion

TABLE 2

COMPOSITION OF THE SKELETON OF A 70-KG. MAN

Percent		Weight in kg.
44	Water	5.4
10	Fat	1.2
14	Na, K, S, CO_2, etc.	1.7
12	Calcium	1.48
6	Phosphorus	0.74
14 (2.2)	Protein (Nitrogen)	1.7 (0.27)

Total body N = 2.1 kg.
N in skeleton = 0.27 kg. or 13%
Ca/N in the skeleton = 5.5/1
N per gm. Ca in bone = 0.18 gm.

hence

storage of 1 gm. Ca in bone requires storage of 1.4 gm. N in entire body

TABLE 3

POSTMENOPAUSAL OSTEOPOROSIS

E.S. NYH 30326 ♀ Age 64

No. 7-day Periods	Intake gm./day		Balance (Average) gm./day				
	Ca .	Sr	Ca	Sr	Ca + Sr	P	N
3	1.480		-0.036			+0.009	-0.53
2	4.210		+0.233			+0.080	-0.17
3	1.482	2.750	+0.164	+0.889	1.053	+0.229	+0.52

(Table adapted from Shorr, E., and Carter, A. C.: *Bull. Hosp. Joint Dis.* **13:** 59, 1952.)

than calcium in a fair number of patients, and may be retained when additional calcium (more than 1.5 Gm.) does not seem to lead to significant retention.

Table 3 shows a reaction illustrative of an unexpected increase in retention of both calcium and strontium. When the patient was receiving 1.5 Gm. of calcium, the calcium balance was negative. When the calcium intake was increased to 4.2 Gm., there was a positive balance of about 0.25 Gm. per day (233 mg.). When the calcium intake was reduced to the original 1.5 Gm. and the difference made up with strontium lactate, considerable strontium was absorbed. There was no interference with calcium storage, which was even more pronounced than during the first period, so that the combined retention of strontium and calcium was appreciable.

We have been studying this measure for many years and are inclined to believe that it is a desirable adjunct in the management of these patients. Unfortunately, one cannot be sure that such a response will occur in each case.

Table 4 shows the data in a patient who was receiving 1.5 Gm. of calcium and storing 92 mg. per day. For three weeks, 1.7 Gm. of strontium daily, as the lactate, was added to her diet. Not only was there no gain, which we had hoped for on the basis of the previous patient's reaction, but there was no change of any kind. A genuine defect was present that was not overcome by merely adding more lime to the diet. We then resorted to the use of estradiol benzoate in a daily dosage of 10,000 rat units intramuscularly. Although receiving the same diet, this patient then absorbed both calcium and strontium. For the following three weeks, a daily dose of 50 mg. of testosterone propionate was added. The storage was highly gratifying—even double the improved storage with estradiol benzoate.

These two hormonal agents, which participate less actively in the economy of the body in this age group, are both helpful. They are often additive in their effects.

TABLE 4

POSTMENOPAUSAL OSTEOPOROSIS

E.P. NYH 250335 ♀ Age 61

No. 7-day Periods	Intake gm./day		Balance (Average) gm./day				
	Ca	Sr	Ca	Sr	Ca + Sr	P	N
3	1.514		+0.092			+0.400	+3.28
3	1.516	1.740	-0.010	+0.075	+0.065	+0.319	+2.66
3*	1.517	1.740	+0.309	+0.231	+0.540	+0.524	+3.44
3**	1.516	1.740	+0.630	+0.473	+1.104	+0.900	+6.28

* Medication: Estradiol benzoate 10,000 R.U. i.m. q.d.
** Estradiol benzoate 10,000 R.U. plus Testosterone propionate 50 mg. i.m. q.d.

(Table adapted from Shorr, E. and Carter, A. C.: Tr. Second Conference on Metabolic Interrelations, ed. by E. C. Reifenstein, Jr. New York, Josiah Macy, Jr. Foundation, 1950, p. 144.)

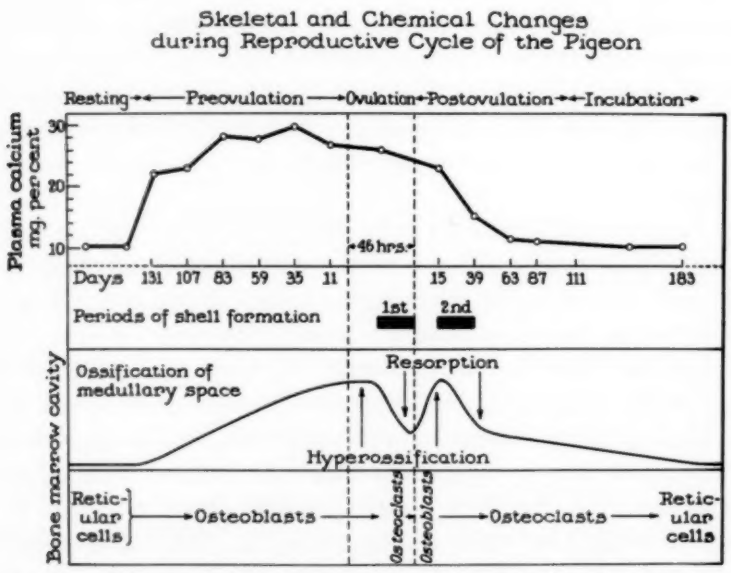


FIG. 7. Estrogen-calcium relationship in the laying of the hard-shelled egg. (Adapted from Riddle, O.; Rauch, V. M., and Smith, G. C.: *Anat. Rec.* **90:** 295, 1944.)

One might ask why estrogen should be related to calcium storage. The only thing I can suggest is that it is a hang-over from when nature developed the ingenious device of a hard-shelled egg, as is shown in Figure 7. In the ovarian cycle of the bird, when the follicle develops, there is more estrogen. The bird

uses this device to store calcium in the bones. After the egg is laid, it takes from this rich storehouse of lime enough calcium to replace that used by the egg. Being mightily pleased witd this mechanism, nature then retained it for the laying of shell-less eggs, including those of the human being.

I mentioned estrogens and androgens, and now we come to vitamin D. Table 5 shows the course of calcium balance in a man who was storing 117 mg. of calcium a day on an intake of 1.5 Gm. He stored 239 mg. (double storage) when a daily dose of 50,000 international units of vitamin D was added. When strontium was added, the storage increased to about 400 mg. With the use of testosterone propionate, it increased to 500 mg. Therefore, vitamin D must also be considered a potentially useful agent.

Table 6 demonstrates another example of the effect of vitamin D. As listed in line 4, the storage of calcium and strontium was 659 mg. a day for four weeks before vitamin D was given. Then vitamin D was given for four weeks, and the storage increased to 807 mg. Then testosterone propionate was given in a dosage of 10 mg. intramuscularly per day (equivalent to about 40 mg. of methyltestosterone orally per day), but no extra storage resulted.

One has to remember that dosage requirements are very important, and are often the limiting factors in the use of these hormones. This is illustrated by the line next to the last in Table 6. Estradiol benzoate, 1,200 rat units a day, was given in addition to the other medications. The minimal change of 36 mg. means that when estrogen and androgen (usually so effective) are given in subeffective doses, it is wasteful for the patient and deluding to the physician.

TABLE 5

OSTEOPOROSIS

J. McD. NYH 530048 (M) Age 66

No. 7-Day Periods	Intake Gm./Day		Balance (Average) Gm./Day				
	Ca	Sr	Ca	Sr	Ca + Sr	P	N
3	1.508		+0.117			+0.107	+0.42
4*	1.508		+0.239			+0.142	+0.95
4**	1.508	1.726	+0.161	+0.247	+0.408	+0.166	+0.61
3***	1.508	1.726	+0.297	+0.282	+0.579	+0.324	+3.16

* Medication: Vitamin D_2 50,000 I.U. q.d.
** " " " 50,000 I.U. q.d.
*** " " " 50,000 I.U. q.d. + Testosterone Propionate 50 mg. i.m. q.d.

(Table adapted from Shorr, E. and Carter, A. C.: Tr. Second Conference on Metabolic Interrelations, ed. by E. C. Reifenstein, Jr. New York, Josiah Macy, Jr. Foundation, 1950, p. 144.)

Table 7 shows that we cannot always predict that vitamin D in a dosage of 50,000 international units daily, will be helpful. In the third line, it may be seen that 394 mg. of calcium and strontium were stored. During the next five

TABLE 6

MORQUIO'S DISEASE

N.G. NYH 541440 ♂ Age 13

No.7-Day Periods	Intake Gm./Day		Balance (Average) Gm./Day				
	Ca	Sr	Ca	Sr	Ca + Sr	P	N
3	0.903		+0.166			+0.140	+0.50
3	1.501		+0.374			+0.203	+1.64
4	1.501	1.730	+0.398	+0.261	+0.659	+0.360	+1.84
4*	1.501	1.730	+0.442	+0.365	+0.807	+0.331	+1.20
2**	1.501	1.730	+0.478	+0.324	+0.802	+0.453	+2.97
2***	1.501	1.730	+0.524	+0.314	+0.838	+0.423	+3.08
4***	3.231		+0.648	-0.123	+0.525	+0.314	+2.19

* Vitamin D_2 50,000 I.U. q.d.
** Vitamin D_2 50,000 I.U. q.d., Testosterone propionate 10 mg.i.m.,q.d.
*** Vitamin D_2 50,000 I.U. q.d., Testosterone propionate 10 mg.i.m.,q.d. Estradiol Benzoate 1200 R.U.,i.m.,q.d.

TABLE 7

IDIOPATHIC OSTEOPOROSIS

R.M. NYH 554371 ♀ Age 19

No.7-Day Periods	Intake Gm./Day		Balance (Average) Gm./Day				
	Ca	Sr	Ca	Sr	Ca + Sr	P	N
2	0.799		-0.036			+0.280	+0.86
2	1.502		+0.047			+0.299	+0.75
3	1.502	1.740	+0.196	+0.198	+0.394	+0.330	+0.27
1*	1.502	1.740	+0.231	+0.108	+0.339	+0.268	+0.29
2*	3.232		+0.471	-0.188	+0.283	+0.346	+0.60
3*	1.502	1.740	+0.110	+0.189	+0.299	+0.327	+0.57
4*	3.228		+0.234	-0.186	+0.048	+0.304	+0.19
2*	1.498	1.740	+0.048	+0.237	+0.285	+0.274	+0.37
4**	1.498	1.740	+0.250	+0.169	+0.419	+0.404	+0.51
4§	1.498	1.740	+0.279	+0.315	+0.594	+0.479	+2.12
7§§	1.483	1.740	+0.341	+0.414	+0.755	+0.394	+1.01

* Vitamin D_2 50,000 I.U., q.d.
**Vitamin D_2 50,000 I.U., q.d. Estradiol Benzoate 10,000 R.U., i.m.q.d.
§ Vitamin D_2 50,000 I.U., q.d. Estradiol Benzoate 10,000 R.U., i.m.q.d. plus Testosterone propionate 50 mg. i.m.,q.d.
§§ Vitamin D_2 50,000 I.U., q.d. Estradiol Benzoate 15,000 R.U., i.m.q.d. plus Testosterone propionate 50 mg. i.m.,q.d.

(Table adapted from Shorr, E. and Carter, A. C.: *Bull. Hosp. Joint Dis.* **13:** 59, 1952.)

weeks, with vitamin D alone, there was no increase in storage—299 mg. as compared with 394 mg. It cannot be predicted in any one patient that the operation of these various agents will be equivalent.

These are enough examples. Now I shall make some general comments on dosages. There is no doubt, and I think all of us working in this field are agreed, that estrogens and androgens are extraordinarily effective when given in correct amounts. We have to ask what those amounts are, and I should like to suggest that it is a rare woman indeed in whom any storage can be achieved with less than 5,000 rat units of estrogen per day. It may be that more benefit will be obtained with 10,000 rat units. For most patients I would recommend 7,500 units a day. In the case of a male patient, such a dosage has certain psychologic effects that must be accepted if the condition warrants it. Also, estrogen can be used in combination with androgen.

The dosage of androgen that we have found effective is the equivalent of 25 mg. of testosterone propionate intramuscularly daily; results are no better with 50 mg. There is little evidence of storage with less than 25 mg. daily (equivalent to 80–100 mg. of methyltestosterone orally).

In women, combined usage of androgen and estrogen may serve to prevent effects on the uterus that are undesirable but inevitable with large amounts of estrogen. However, we must accept the likelihood of bleeding, and should interrupt such bleeding every month by giving progesterone in the active oral or intramuscular form. Our standard practice is to give 100 mg. of ethisterone orally for five days every month. This produces definite bleeding of modest proportions, which results in adequate shedding of the endometrium that has been built up, and allows the patient to have the benefit of continued therapy with estrogen.

The addition of lime salts to the diet is desirable. These salts offer something the patient often lacks. It should be pointed out that there seems to be some evidence that strontium lactate is often better absorbed than equivalent amounts of calcium.

Vitamin D, when added to the foregoing regimen in amounts no greater than 50,000 international units a day, is often, although unpredictably, effective in increasing the retention of calcium.

Thus, for the treatment of osteoporosis, we have recommended: 1) an adequate diet which fulfills the needs for protein, calcium and calories—a diet that often taxes the ingenuity of the doctor in view of the eating habits of the patient; 2) supplementation of the diet, either with lime salts or calcium or strontium; 3) the use of androgens and estrogens in effective amounts; and 4) as much activity as is consistent with the patient's capacity.

We appreciate the opportunity to talk to a group such as this. You will be able, more effectively than any other group, to implement the investigative work of the panel members, by direct application to the patient.

REFERENCES

1. a) Lewin, I., and Spencer, H.: Calcium tolerance test; an indicator of bone metabolism and of the effects of therapy thereon, (abstract) *Cancer Research* **12:** 278, 1952. b) Laszlo,

D., AND SPENCER, H.: Newer techniques in the study of calcium metabolism in man and effects of hormones thereon, *in* Hormones and the Aging Process, ed. by E. T. Engle and G. Pincus. New York, Academic Press Inc., 1956.

2. SPENCER, H.; LEWIN, I., AND LASZLO, D.: A simple test to study calcium metabolism in endocrine disorders, (abstract). *J. Clin. Endocrinol. & Metab.* **13:** 861, 1953.
3. DEITRICK, J. E.; WHEDON, G. D., AND SHORR, E.: Effects of immobilization upon various metabolic and physiologic functions of normal men, *Am. J. Med.* **4:** 3, 1948.
4. HOWARD, J. E.; PARSON, W., AND BIGHAM, R. S., JR.: Studies on patients convalescent from fracture. III. The urinary excretion of calcium and phosphorus, *Bull. Johns Hopkins Hosp.* **77:** 291, 1945.
5. WHEDON, G. D.: Calcium loss in paralytic poliomyelitis and its quantitative relationship to the development of demonstrable osteoporosis, *J. Clin. Invest.* **31:** 672, 1952.
6. WHEDON, G. D.; DEITRICK, J. E., AND SHORR, E.: Modification of the effects of immobilization upon metabolic and physiologic functions of normal men by the use of an oscillating bed, *Am. J. Med.* **6:** 684, 1949.
7. WYSE, D. M., AND PATTEE, C. J.: Effects of the oscillating bed and tilt table on calcium, phosphorus, and nitrogen metabolism in paraplegia, *Am. J. Med.* **17:** 645, 1954.
8. BOGDONOFF, M. D.; SHOCK, N. W., AND NICHOLS, M. P.: Calcium, phosphorus, nitrogen, and potassium balance studies in the aged male, *J. Gerontol.* **8:** 272, 1953.
9. BOGDONOFF, M. D.; SHOCK, N. W., AND PARSONS, J.: The effects of stilbestrol and the retention of nitrogen, calcium, phosphorus, and potassium in aged males with and without osteoporosis, *J. Gerontol.* **9:** 262, 1954.

GERIATRICS—A DEFINITION*

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The practice of geriatrics is the practice of medicine among older patients with their special kinds of disease and their special variants of the usual diseases. There is no question of the nature of this discipline as it deals with the actual patient. But geriatrics as a study is a little wider than that. We would otherwise be like the simple, happy mechanic who knows what to tighten but "has no time for the theory of the thing."

Aging people have attracted a surprising number of well-wishers in recent times, who have pre-empted whatever aspects of the problem seemed to be unattended. We can use help from everyone, but we have this problem to deal with firsthand. Thus the "biology" of aging is no longer supposed to concern us—as if one could deal with pneumonia without a thought of bacteriology. Likewise the "sociology" of older people has suddenly touched many hearts—as if your patient lived in Nirvana up to the moment of his 65th birthday and then became a pitiable object. This is disingenuous. I cannot think of an age, younger or older, when the emotional difficulties, problems of living and working, and the economic predicament of a patient are not profoundly involved in the practice of medicine.

Another exercise is to define aging, and still another is to conjecture whether it is a consequence of disease in later life or the aggregate of all injuries and disabilities during a lifetime. These efforts have produced a voluminous literature, if they have not done much to help older people. It is regrettable that physicians themselves have participated in this largely verbal "research," though it is understandable, since the focus of attention and effort is naturally the patient's illness: we see the trees, but we do not look at the soil. The various clinical entities are much more obvious than the aging process that underlies them and makes them possible, and they produce injury as a third-order phenomenon that is then misapprehended as "aging." The three orders of effect intended seem to be those of 1) age, 2) specific diseases, and 3) the disabilities of specific disease. I think we can be more sophisticated than that. Crampton (1) says, "Our chief enemy is not age; it is damage." Yet even he has gone on to enumerate efforts to defer aging, such as encouraging activity, administering Rauwolfia, and praising religion, without closely considering "damage" or how it came about.

If we can grant our respect only to a well-defined clinical entity like hypertrophy of the prostate, let us define an "aging syndrome" with its own etiology, pathogenesis and pathognomonic features, so that it can receive as much notice as it deserves—like Paget's disease, or hypertension—and then perhaps some-

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thing can be done about it. The syndrome is not highly distinctive: the history shows that the patient was born some time ago, and physical examination may show that the hair is graying. These two findings are pathognomonic. The farther you probe the less you can find, until you come to the pathology. That is, "The criteria of age vanish more and more, as dissection progresses inwards and into histological details" (2, 3). Pathologically, there is nothing, except in the nervous system—at least there is little of consequence. Carlson (4) enumerated among the findings "very gradual but significant" shrinkings, enlargements and atrophies of all kinds with their functional counterparts. The latter are evident only in respect to acuity of hearing and vision; these decline from about the age of 30 years. Within the nervous system the findings are chiefly loss of neurons and the accumulation of argentophil material in the cytoplasm (5a). As a neuron is the one variety of nonmitotic cell, it would be anticipated that some diminution in numbers would occur during the life span. Yet the nervous system is the one system that shows few operational effects of age; the loss of a few neurons has surprisingly little effect (6). This is stated in awareness of Lehman's (7) impression that "the brain slowly loses its powers after the age of 37 . . . especially when considerable genius is involved in a man's work, he is likely to reach the peak of his accomplishments around the age of 30." Many of the recognized geniuses belong to olden times and died in their 30's of such diseases as tuberculosis. As their latter work was naturally among their best, it would appear (and no doubt this caused Lehman to think) that their greatest achievements were consummated around the age of 30 to 35 years. There being no way of knowing what Chopin, for example, would have composed at age 70, Lehman cannot be gainsaid, except by pointing out that it appears that geniuses who do live beyond 30 or 35 years continue to be productive—Einstein, for one. Unusual achievements are striking in youth, but certainly are not limited to youth.

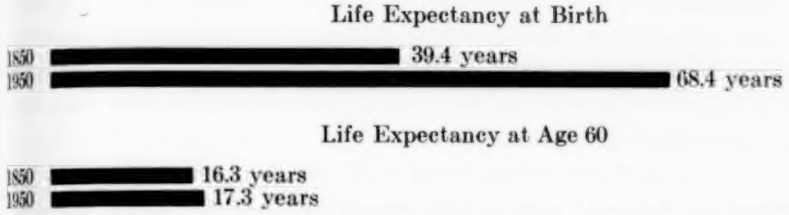
Ideas contrary to those of Lehman are abundant: for instance, Hirsch's (2) "sort of sublime 'presbyopia' which is the root of universality of views and judgment and is called the wisdom of the grand old men." True, it is possible that the "wisdom" of tribal elders was that of superannuated lads of almost 30, and that continuing the cultural practice of harkening to the grand old men, who today are upwards of 50 years at least, is what has brought the world close to utter destruction. But here it is unlikely that age alone governs.

Returning to the "aging syndrome," it is so intangible that no one is permitted to die of it. A specific disease has to be mentioned or the matter is unscientific. Thus the biologist defines aging as a process that invariably terminates in death. The definition can be formidable—"a process of unfavorable progressive change, usually correlated with the passage of time, becoming apparent after maturity and terminating invariably in death of the individual" (9). The medical examiner rules, however, that such a thing cannot happen.

We can be sure that when more has been done about the specific diseases, patients will finally have a right to die of the aging syndrome. In the meantime, some clear idea of the syndrome and how it creates a susceptibility to the diseases of later life will afford some means of controlling one as well as the other.

The challenge is enormous, as the whole project lies before us. It may be that the difficulties are exaggerated. In other branches of medicine, such as pediatrics or obstetrics, the effort is to remove any disturbing process and let nature take its course. Here, the natural course is unacceptable and so we judge that it must be uphill work. It may seem that nothing at all can be done.

So far nothing *has* been done. There has been a steady gain in life expectancy which is widely misinterpreted as a change in the life span. Nothing has increased the life span significantly. More people *are* surviving the infections and other disasters of early life, so that there are more people who live to be 60 years of age. In general, there are simply more people, but they do not live any longer beyond the age of 60 years than ever before. This may be shown graphically as follows:



(These data are from the Statistical Department of the Metropolitan Life Insurance Company, New York) (10).

There has also been a temporary decline in the birth rate, but this is a fruitless way of giving the illusion of longevity. No one has yet succeeded in adding years to life at the time of life that interests us. "Altogether our progress with the diseases of late maturity and old age has not been of any consequence. To date, we have not been able to extend the life span (5b). The motto, "To add life to years, not just years to life," implies that there is some way of adding years, but that it is despised as not enough to have done.

So distinguished an observer as Dublin (5b) once calculated that life expectancy might gain by nine or ten years without cardiovascular-renal disease, but then immediately confessed the figures were "academic" and the expectation "quite impossible" because "the processes of degeneration are inevitable." Now it is easy to imagine another world where the physiology of aging is understood but where no one has stumbled on anti-infective agents (as twenty years ago we had not). In such a world an author could write that people might live longer were it not that "infection is inevitable." One writer (11) declared that "We cannot stop aging," and then, probably getting the cart before the horse, proceeded to say: "To do so would be to terminate life." Aging is called "part of living" (11); and this is true, much as cholera is part of India. I do not see how an assumption that one can do nothing is going to advance this problem. We have to achieve some concept of what this thing is, its magnitude, when it starts, and where it lies.

Von Albertini (9b) has declared that aging "is a problem of balance between loss and regeneration." It occurs at that point where catabolism catches up with anabolism. It is the point at which cells no longer divide (5c); it begins where growth ends. It used to be an epoch of poor homeostasis, but with changing

fashions it has become a result of poor adaptation (8c). These are all notions attempting to define aging in familiar but excessively general terms; since they are inaccurate and introduce no genuine datum, they remain largely conversation.

However, Lansing cites work with unicellular organisms and insects, and with rats (C. M. McCay) (12), showing that handicaps in early life which postpone growth can increase longevity. This line of experimentation, and other evidence, may well suggest that an embryonal cell is endowed with a closely allotted potential (for clarity, it might be conceived as a quantity of substance, although actual preformed substance would amount to tons per cell) that is progressively dissipated throughout the lifetime of the cell and (to a lesser extent) of its daughter cells. This potential might be likened to a tightly-wound spring. Mitosis or conjugation reorganizes the cell (or "restores some material"), adding some new tension to the spring. A model is extremely hard to establish, because the potential resides in the workings of an unidentified nuclear structure that is continuously developing material, though at a nonuniform rate. We can, however, localize it and recognize a part of its behavior.

It is possible to draw a curve representing some (any convenient) metabolic function from conception to old age—let us say the addition of tissue mass per unit weight of the organism. It is the widely applicable biologic or exponential curve $x = e^{-y}$, and although it is not a complete description of aging, it will show the factor in which we are interested. Obviously, the synthesis of protoplasm *in utero* is enormous, but in the growing child it has fallen off markedly, and in adult life has a net value near zero. The function is declining most rapidly when its value is greatest. We may think of a decline in metabolic activity as characteristic of advancing age, but by far the sharpest decline occurs *in utero*, and it is the fetus that ages most rapidly. This is an old (13) and obvious idea. It is so fundamentally correct that it has been thoroughly disputed, as when Lansing (9a) says, "The fetus is not aging, as I see it; it is not losing vitality; it is not degenerating rapidly." The interesting part of the curve is at the ages of 50 and 60 years, at which times it can be seen that the decline is exceedingly small. Later life is a time of remarkable metabolic stability. What strikes the eye clinically is an integration of losses over a period of many years, but "as you see it" this is not the *rate* of the process. On the contrary, the decline is small, almost to vanishing, after the age of 20 or 30 years; and at 50 or 60 years (when its effects are most apparent), the smallest possible interference would be enough to reverse the aging process.

Intrinsic aging, apart from supervening illness, is not an active process. If a patient can reach this slope at age 60 years he is, mathematically speaking, no worse off at 100 or 1,000 years. There is nothing here that identifies 100 years as a probable limit of the life span, even for the average individual. I emphasize that this is an idealization, but it will do. When Dublin (5b) says that ". . . nature has allotted to man a life span of about 100 years," the grounds for his deduction are unclear.

One of our problems is to decide what biologic activity is chiefly concerned in such a curve. I think we no longer need contemplate the loss of some obscure

reparative function of the connective tissues (the scavenging theory), the accumulation of insoluble materials like calcium in the cell (the boiler-scale theory), the intoxications that are caused by malevolent bacteria (the rancidity theory), and that can be overcome by friendly organisms (the yogurt theory), the specific transmissible principles that directly cause aging (assassination theory), and similar concepts. Today metabolic events are read in terms of cellular enzymatic function, and even though we have only the crudest, early grasp of that machinery, we are obliged to visualize the aging process in such terms. The suggestion is no longer daring, and not yet banal. Perhaps after another ten years it will sound as absurd as some of its predecessors, but this is where we must now think of the problem.

For example, we speak of elastic fibers in the aorta as undergoing "involution" because there are fewer of them. In the still-life picture we have from pathology, some of the fibers that were present from birth have unfortunately disappeared; but we know better. We know that *all* the fibers dwindle away on a weekly or monthly basis and are reconstituted at about the same rate from commonplace raw materials that are easily obtained. They are produced by living fibroblasts that are about as numerous and functional at one age as at another. It is no mystical process, but enzymatic activity, that produces them—in the same manner as anything else produced in the organism. Now if the activity of these cells were slightly diminished, perhaps to the extent of 1 part in 10,000, then by the end of twenty years the "loss" of elastic fibers would come to 10 per cent and the histologist could see it. This is the magnitude of aging. Unfortunately one cannot see, or detect chemically, changes of the order of 1 part in 10,000 (or even 1,000), and for this reason the metabolic changes of advancing age cannot be specified like those of surgical shock.

No doubt every germinal cell contains, not a huge metabolic equipment, but a huge potential for developing cellular machinery in every ultimate, adult body cell (5c); and the ultimate cell still contains such a potential for its thousands of descendants during a lifetime. When the generation of enzymatic material in particular cell types falls off to the extent of 1 part in 1,000, this decrease can be localized in at least a rough way, by exclusion. The difficulty lies below the level of the gene. We have no reason to think a gene in any non-neoplastic cell can "wear out." It transcends the supply of protein-forming nutrients, usually abundant at any age, or the supply of prosthetic groups (vitamins), else we should have seen a doubling of the life span in the past few years.

We have merely to identify the operations and chemistry of the several templates that form a hierarchy between the gene and the cellular enzyme, or, in other words, solve the problem of how nucleic-acid configurations ultimately govern the synthesis of cellular proteins. This is difficult at present, almost to the point of total impossibility; but we may have the critical information by next week or next year. We may then find, as it has been suggested, that so simple a procedure as feeding certain precursor materials massively will be enough to exert that small degree of interference that has been mentioned, as indeed it has been shown in the guinea pig. Needless to say, it defies demonstra-

tion in man, nor is it likely to be so simple. But a part of your Society, the American Geriatric Research Foundation, is interested in clarifying this among other matters (10).

As to these cellular mechanisms that concern us, we are obliged to examine the state of affairs after the processes have been stopped and stained with hematoxylin-eosin, and to make some limited deductions from chemical assay during life. Yet the lack of detail does not place a working model beyond reach. Physicists are having trouble with the wave theory *vs.* the corpuscular theory of light; under either heading they can be articulate, but are at a loss for a complete concept. Regarding the biology of the cell, we have the opposite trouble—the concept can be assembled from what data we have, but its articulation is difficult. We have to go part of the way with one model, then translate it into another, repeatedly. One can entertain the idea that the high early cellular potential in our derivative curve is like a fully wound spring: then, within limits, one can conceive of some rewinding with every mitosis; but the initial tension can never be reached in any cell but a fertilized ovum. There is always a lower and lower potential (and we are *not* speaking here of entropy). Now, if we can translate the potential into—not material, but nuclear organization capable of developing material, we shall envision physiologic processes and actual substances concerned in aging phenomena rather than the intangibles and intuitions engendered so far.

Whereas early investigations of cellular workings were focussed on proteins as the immediate functional moieties, it is clear that materials which organize the proteins into their working configuration stand one level higher, and that gene materials are prior even to these. Our model for aging demonstrates changing capabilities at this intermediate level. Each aspect of the model, however, has to be reinterpreted as a dynamic system having perpetual turnover; it does not stand still as does a histologic picture. Though we are beginning to have an idea of the chemical structure utilized at these different levels, our chemistry is too rudimentary to account for specific details of the mechanisms; that is more physics than chemistry. However, there is enough to work with, and some of the particulars will be discovered soon.

To conclude this definition of geriatrics, if that is what it is, I would invite you to consider among the diseases of later life a nondisease state known as the aging syndrome so that, without disputing whether there is any such thing, we can set about dealing with it. There is as good reason to be optimistic about influencing this process as any of the specific diseases which we are supposed to be able to manage.

REFERENCES

1. Crampton, C. W.: Medical services in aging and de-aging, *New York State J. Med.* **54:** 2844, 1954.
2. Hirsch, S.: A clarification of basic concepts in gerontological research. Third International Gerontological Congress, London, July, 1954.
3. Lansing, A. I., *in* Gross, J., ed.: Aging of connective tissues. Problem identification (2nd Internat. Gerontol. Congr., September 1951), *J. Gerontol.* **7:** 585, 1952.

4. Carlson, A. J.: Gerontology. The how and why of ageing, *in* Alexander, J., ed.: Colloid Chemistry. New York, Reinhold Publ. Co., 1944, Vol. 5, p. 1051.
5. Lansing, A. I., ed.: Cowdry's Problems of Ageing. Biological and Medical Aspects, Baltimore, The Williams & Wilkins Company, 1952: (a) O'Leary, J. L.: Ageing in the nervous system, p. 223; (b) Dublin, L. I.: Longevity in retrospect and in prospect, p. 203; (c) Lansing, A. I.: General physiology, p. 3; (d) Cowdry, E. V.: Ageing of individual cells, p. 50.
6. Weinberg, M.: Mechanism in neurosis, *Am. Scientist* **39:** 74, 1951.
7. Lehman, H. C.: Age and Achievement. Princeton, N. J., Princeton University Press, 1953.
8. Alvarez, W. C.: At what age do men do their best work? *Geriatrics* **9:** 446, 1954.
9. Lansing, A. I., ed.: What is ageing? Panel discussion (2nd Internat. Gerontol. Congr., September 1951), *J. Gerontol.* **7:** 452, 1952: (a) Lansing, A. I.: p. 453; (b) Von Albertini, A.: p. 452; (c) Jensen, J.: p. 453; (d) Warthin, A. S.: Pathology of aging processes, *Bull. New York Acad. Med.* **4:** 1006, 1928, cited by Korenchevsky, V.: p. 456.
10. Prospectus, Am. Geriatric Research Foundation, New York, September 1953.
11. Steiglitz, E. J.: Geriatric Medicine, ed. 3. Philadelphia, J. B. Lippincott Co., 1954, pp. 3 and 10.
12. Lansing, A. I., ed.: Cellular aging. Panel discussion (2nd Internat. Gerontol. Congr., September 1951), *J. Gerontol.* **7:** 602, 1952.
13. Minot, C. S.: The Problem of Age, Growth, and Death. New York, G. P. Putnam's Sons, 1908.
14. Speaker, D.: (National Foundation for Anti-Aging Research): Personal communication.

THE CHALLENGE OF OUR AGING POPULATION*

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It is a privilege to bring you greetings from our American Geriatrics Society. On behalf of the Society, I most heartily felicitate you on the great work upon which you are just embarking.

Two incidents were operative in bringing me here tonight—the thirteenth annual meeting of the American Geriatrics Society, and a luncheon with Dr. Priddle. The first is important because of the number 13; no one else would take a chance on the presidency in its thirteenth year. The second is important because it was during this luncheon with Dr. Priddle that I realized that not I, but the President of the American Geriatrics Society, was being asked to join your group this evening.

I am very new to the position of President (this is the sixth day), and fear I can do justice neither to the Society nor to the very broad subject of geriatrics. I feel indeed like the very nervous bridegroom at the wedding supper who, after much insistence that he make a speech, rose timidly, and fondly placing his hand on the bride's shoulder, said "This has been forced upon me." Geriatrics is the bride and no matter how I feel about her, she is at all times somewhat overwhelming and occasionally, if I may say so, demanding.

The challenging need for action in the field of aging needs no other emphasis than that to be placed upon the overall increase in the population of the world and the continually expanding percentage of people who live to be 65 and over.

STATISTICS

The latest available figures from the U. S. Census Bureau indicate that since 1900 the number of persons in the United States who are 65 years or over has quadrupled, while the population has only doubled. In one New York State community, 20 per cent of the residents are 65 years or over; in 30 cities of the State, more than 10 per cent of the residents are above that age; and the average percentage for the entire state is 8.5 per cent. Let us consider some figures for the United States as a whole. There were about 2.5 million people over 65 in 1900, and around 12 million in 1950. During this same period of time the population has approximately doubled.

The vastness of the problem may be emphasized in yet another way. Seven per cent of the earth's 2.5 billion population are now over 65 years of age. These 175,000,000 people are more than the total United States population, are greater in number than all of the inhabitants of all of the countries in South America, and are about seven times the number of people contained within the Roman Empire at the height of its glory.

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† President of the American Geriatrics Society, 1956–1957.

Let us view these data from yet another angle: in 1900, the average life expectancy was approximately 45 years, but today it is approximately 69 years—an increase of 24 years. Although it is true that much of this increase has been achieved by a markedly decreased infant mortality, some credit must also be given to the advent of antibiotics, improved nutritional standards and the ready availability of nutritional supplements.

The problems of aging are also inseparably linked with our social structure, including its retirement ages, its pension plans and its ever increasing population pressure. For example, in 1900 a man of 20 could look forward to 39.4 years of working life and 3.8 years of retirement, making a total age of 42.2 years. In 1950, this man would have had 43.2 more working years, leaving 5.7 years of retirement. If a man in 1900 achieved the age of 60, he could expect 14.3 more years of life, with 11.5 devoted to work and 2.8 to retirement. By way of contrast, in 1950, he would have 15.7 more years of life, of which 9.7 would be spent working and 6.0 in retirement. Not only have the average age and the average working span of life materially increased in this period, but the time spent in retirement has actually doubled.

Where are these 12 million people over 65, a major portion of whom are not profitably employed? Nearly 90 per cent are in their own homes or those of immediate relatives. Not quite 7 per cent are in what is commonly called "old peoples' homes." Approximately 4 per cent are in private residential homes, primarily designed for old-age pensioners.

Unless these people are self-supporting, or cared for by insurance or other plans, they often become a burden on the immediately succeeding adult generation.

This tremendous increase in the number of people over 65 poses some difficult problems. In the present state of society—and knowledge—we are not as well equipped to solve them as we should be. Nevertheless, to be aware of the situation is a good start, for awareness must precede investigation and investigation must precede definitive action. In your meeting tonight, the emphasis upon investigation presages early action.

In extending his invitation to be with you, Dr. Priddle emphasized that I should try to tell you what is going on in the field of aging in your neighboring country to the south. This is a big order, and I am sure many things will escape even passing mention.

PROBLEMS OF AGING IN THE UNITED STATES

National and local welfare organizations

In the first place, it can scarcely be said that there is any nationwide concerted attack on the problem at a national level. However, through the federal government, some national voluntary organizations have been created. Among these should be mentioned the National Committee on Aging and Geriatrics, formed shortly after the First National Social Welfare Assembly, from which have come profitable discussions and suggestions over a period of several years. The National Institutes of Health are now preparing to sponsor a national research program, but the details of this have not as yet been fully worked out.

In keeping with the traditions of free enterprise—traditions which you hold as sacred as we do—and working through the foregoing types of organizations and many additional national and local voluntary organizations, modest but positive advances have been made in studying the problems, in training workers and in responding to the demand that older people be served as individuals who can not only be helped by such activities, but also can continue their service to others.

It is believed that a large proportion of our 12 million people over 65 can be profitably employed. Already, the New York State Education Bureau and several private agencies have established retraining centers for the elderly; at the same time, outlets for re-employment are being sought.

Scientific societies

What scientific societies exist in the United States for the study of problems of aging? Two are exclusively devoted to this field—The Gerontological Society and the American Geriatrics Society, the latter of which I have the honor and privilege to represent. The scope of the Gerontological Society includes all aspects of the process of aging. Three major sections of activity can be recognized in the work of this organization: 1) the psychological and social sciences, 2) the biological sciences, and 3) clinical medicine.

The American Geriatrics Society focuses its attention upon the prevention and treatment of diseases of the aged, but recognizes through associate memberships the role of the social sciences. Its major function is the dissemination of, and interchange of research and clinical knowledge among its members, and through them to the profession at large.

Several other scientific bodies in the United States have as their sole objective a study of one or more diseases common to the aged. Among these are such organizations as the Society for the Study of Atherosclerosis, the American Rheumatism Association and its component local organizations, and the American Heart Association and its locally affiliated bodies.

Medical schools

Because of our increasing population, the broadening span of life, the greater precision of experimental tools, and the increase in money available from industry, government, and private individuals, research in the field of aging is moving forward at a pace which would have been inconceivable even in the twenties or thirties of the present century.

Furthermore, there is an increasing recognition of the field of gerontology on the part of our educational institutions and their affiliated hospitals. Several leading medical schools in our country have established Departments of Gerontology or Geriatrics. The New York State Medical Society is this year strongly urging the American Medical Association to encourage every medical school to create such departments. Those medical schools which have not yet done so, are including members on the faculties in their various departments with a particular interest in this epoch of life.

Hospitals

The Department of Hospitals of the City of New York now has two hospitals representing a total of 5,000 beds solely devoted to a study of chronic disease. In one of these, housing 2,500 people, more than 98 per cent of the patients are over 65 years of age. The latter institution, Bird S. Coler Hospital, is directly associated with the New York Medical College as part of the "New York Medical College, Metropolitan Hospital Medical Center," and it is from this institution that our own experiences with aging have been largely derived.

Basic research

Along what avenues can biologic research proceed most profitably today? A few questions may serve to illustrate both the breadth and the depth of the problem. Can we prevent aging from becoming senility—that morbid state which today all too routinely makes the oldster a complete burden on society through its assault upon the mental integrity of the individual? Can we influence the degenerative diseases which go with aging? Can we maintain the vigor and perspective of middle life into old age?

Although the evidence is still fragmentary in this rapidly expanding field of gerontology, some real progress has been made. The following are a few examples.

Severe phases of hypertension have long defied all methods of approach. Some critical experiments are now in progress which may afford knowledge with which to check this monster, hypertension. Dr. Kinsell at the Institute for Metabolic Research in Oakland, California, has shown that a diet composed mainly of high-quality vegetable fats may influence favorably the vascular changes associated with hypertension as well as with the aging process. Dr. Barr at Cornell University has demonstrated a favorable effect of female sex hormone on some of the underlying changes which accompany hardening of the arteries in the aging. It should be emphasized that these experiments were not originally devised as clinical approaches to these disease processes. They were merely part of investigations into the nature of fundamental biologic processes and the influence of everyday physiologic mechanisms upon them. In this manner, probably, will many real advances be made in the field of gerontology.

We need more studies of biologic indices. Here the field is very broad. Well compiled and analyzed case histories will tell us much. This is a long-term study and should probably cover not only one, but three generations of activity. We are entirely in the dark as to the influence of childhood diseases and nutritional errors on the aging processes; nor can we predict the role of a wide variety of experiences of the young vigorous adult upon the way in which he ages. A series of longitudinal life studies may clarify this. A single illustration will serve to indicate its importance.

Some years ago, Lansing subjected rats aged from 16 to 23 days to relative, but not complete, protein starvation. This age corresponds well to that of human beings of middle and late adolescence. These animals were retarded as to growth rate during the period of the experiment, but promptly caught up with their litter-mate controls when an adequate diet was reinstituted. Moreover, their

behavior and activity could not be distinguished from those of their litter-mate controls until they had attained old age. It was then found that these test rats in old age were less active and in poorer condition than their litter mates and died at an earlier age.

It has often been confirmed that older people do not handle certain nutritional elements as well as younger individuals. It takes more protein to keep the oldster in protein or nitrogen balance—thus allowing for tissue repair instead of wasting. If only average amounts of vitamins, particularly B_1 and C, are given to the aged individual he is likely to have subnormal amounts of these materials in the blood and tissues.

It is well known that the function of all the endocrine glands (beginning with the sex glands) wanes during old age. Replacement therapy, particularly in the case of the thyroid, enables older people to achieve a greater interest in life and to improve their capacity for work and intellectual pursuits. In fact, under the influence of hormones, there is often a much better utilization of protein for bodily repair, so that nitrogen equilibrium is restored in association with an otherwise marginal or inadequate diet.

What is needed in the further pursuit of these problems of aging? What can you, as the Ontario Geriatrics Research Society, do about it? The field is vast, the workers are few, and beyond our present vision lie ever-enlarging vistas and more enticing horizons. Education concerning the needs and basic research in the field are the most important immediate objectives. When Langmuir first joined the then-young General Electric Company's Research Division a good many years ago, he was allowed to choose the subject upon which he would work. To the surprise of his superior, he came back after several weeks of investigating the plant and its facilities and asked to be allowed to study monomolecular films. This had no conceivable application to the everyday production of the company at that time, which was mainly concerned with turning out electric light bulbs and electric motors. However, he was allowed to pursue this "hobby." The result? Among other things, there was the replacement of the old carbon-filament light bulb by the tungsten-filament bulb with its manifold increase in efficiency and longevity.

I emphasize then that basic research in all aspects of aging should be fostered. As soon as a clinical application becomes apparent, private industry is more than anxious to join; but private industry should be encouraged to support basic research as well.

The difficulty arises in finding top-flight thinkers in the field who can spare the time to direct such research. We need those who have met the problems of aging and who, from the pinnacles of their own experience, can choose avenues of approach which are liable to be most fruitful. These investigators, in turn, can inspire and direct workers in a variety of disciplines. In our country, industry, although accomplishing something in the field of basic research, can not do enough to be wholly effective. Governmental agencies can legitimately carry only a part of the burden. It remains for private individuals and voluntary organizations to do the rest.

A word of caution. One must not expect results too rapidly. Money will be needed—much and frequently. At first, results will be meager and only infrequently ripe for immediate practical application.

I wish you Godspeed in the tremendous tasks you have set for yourselves in the Ontario Geriatrics Research Society.

"Coming together is a beginning;
Keeping together is progress;
Thinking together is unity;
Working together is success."

HYPERSPLENISM IN GERIATRICS

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Inasmuch as the normal activities of the spleen have not yet been clearly defined, confusion has resulted from the use of the term hypersplenism. In general, hypersplenism implies abnormal splenic activity with a resulting diminution of some or all of the cellular elements of the blood. The mechanism is not clear and none of the theories which attempt to explain the condition has received universal acceptance. Notwithstanding the controversy, the concept of splenic inhibition of the release of cells from the marrow has been adopted by us because it affords a simplified approach to this unsettled problem. This working hypothesis is presented and examples pertinent to geriatric medicine are given.

The rise of all cellular elements in the blood which follows splenectomy in man demonstrates the participation of the spleen in regulating red cell, white cell (granulocyte) and platelet levels. The existence of a splenic "hormone" which regulates the release of mature cellular elements from the marrow has been postulated (Fig. 1). If one accepts this "hormone" theory, then the reduction in cellular elements in the blood exhibited by some patients with an enlarged spleen may be explained on the basis of overproduction of splenic "hormone." Excessive "hormone" leads to excessive marrow regulation and as a consequence the release of mature cellular elements is inhibited (Fig. 2). The blocking effect would also account for the accumulation in the marrow of normal precursors of the respective elements lacking in the blood, a situation that may be thought of as wealth in the marrow with poverty in the blood.

Such a concept of inhibitory hypersplenism correlates the three cardinal findings in the hypersplenic syndrome: 1) paucity of erythrocytes, granulocytes and thrombocytes in the blood (singly or in any combination); 2) the finding in the marrow of increased numbers of normal precursors of the cellular elements deficient in the blood, and 3) enlargement of the spleen.

The logical conclusion that splenectomy will correct the hematologic changes of hypersplenism is borne out clinically. Anticipation of successful results is predicated on an accurate preoperative diagnosis based on fulfilling the requirements of the diagnostic triad.

MANIFESTATIONS OF HYPERSPLENISM

More detailed characterizations of the syndrome are:

Blood

Anemia, granulocytopenia and thrombocytopenia may be present singly or in any combination. The coexistence of all three is termed pancytopenia. The

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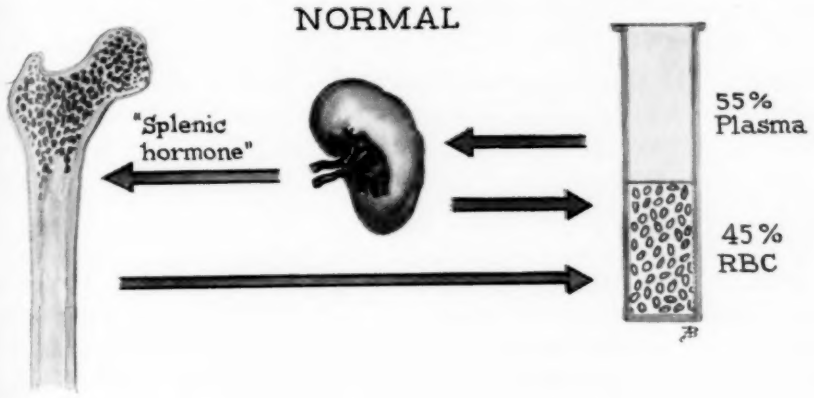
degree to which the cellular elements in the blood are lowered is not correlated with the size of the spleen, and the severity of their depression is usually out of proportion to that which might be anticipated from the underlying disease alone.

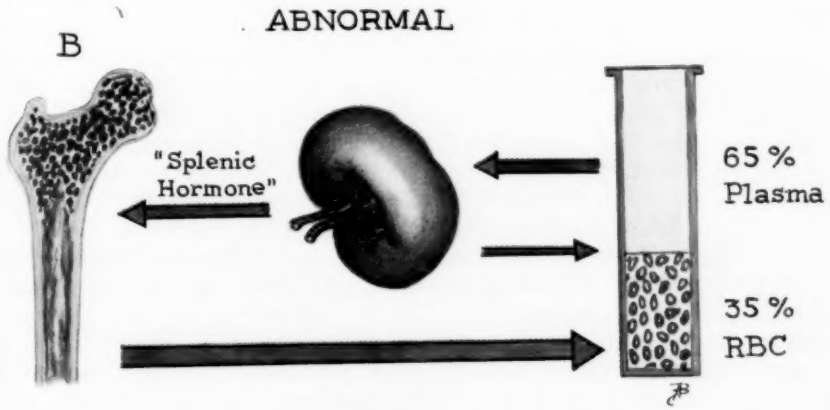
Anemia. In most instances anemia is normochromic and normocytic in type, but occasionally its type may coincide with that of the underlying disease. Mild to moderate degrees of anemia are the rule.

Granulocytopenia. Values substantially below the normal lower limit of 3,000 granulocytes per cubic millimeter are common. Since most granulocytes are



SPLEEN	BLOOD
1. Produces a "hormone" which regulates normal maturation and release of cells from marrow	1. Like a mirror—reflects what happens in the spleen and marrow
2. Removes effete cells	2. —and acts as a vehicle to carry "splenic hormone" and formed elements

FIG. 1. Schematic presentation of how the spleen maintains a balance between the marrow and blood.



"Sequestration" of Formed Elements During Circulation in Spleen

FIG. 2. Schematic presentation of the effect of excess splenic "hormone" on cell release from the marrow, resulting in a paucity of cells in the blood, and a plethora of cells in the marrow.

neutrophils, the term neutropenia is used interchangeably with granulocytopenia.

Thrombocytopenia. The platelet counts are usually moderately depressed, by from 60,000 to 150,000, and it is uncommon to see profound depressions. Because there is no accompanying vascular abnormality, such as is usually seen in other thrombopenic states, hemorrhagic manifestations are rare.

Marrow

The marrow is hypercellular, and the precursors of cells that are at a low level in the blood are found in increased numbers. Thus, proliferation of young granulocytes is seen in granulocytopenia, increased erythropoiesis in anemia, and large numbers of megakaryocytes in thrombocytopenia. The marrow may show no change other than hypercellularity. On the other hand, it may be involved in addition by (a) granuloma, as in tuberculosis, sarcoidosis, histoplasmosis, or Hodgkin's disease; (b) lipoid reticulosis, as in Gaucher's disease; or (c) lymphomas and leukemias (giant-follicle lymphoma, lymphosarcoma, lymphatic or myelogenous leukemias).

Spleen

The spleen may vary in size from 250 grams (just palpable) to huge enlargement. Splenomegaly may be due to: 1) reticulo-endothelial hyperplasia, 2) congestion, as in splenic-vein hypertension (cirrhosis) or splenic-vein obstruction, 3) local disease, as in sarcoid, lymphosarcoma and Hodgkin's disease, 4) infection, such as bacterial endocarditis, infectious mononucleosis, rheumatoid arthritis, tuberculosis and malaria, or 5) generalized disease, such as Gaucher's disease, lupus erythematosus disseminata, leukemia, hemolytic anemia, Hodgkin's disease and myeloid metaplasia. Occasionally, the hypersplenic manifestations may be relieved by medical treatment of the underlying disease.

SIX ILLUSTRATIVE CASES

Case 1

A. P., a white woman, aged 67, with arthritis of one year's reported duration, had been given 13 weekly injections of gold. She had also been treated intermittently for anemia. She was admitted for transfusions because of "aplastic anemia due to gold therapy."

Physical examination. The patient was pale. Scattered petechiae were present. A systolic apical murmur was heard. The spleen was enlarged 2 cm. below the costal margin.

Hemogram. The red blood cell count was 2.01 million; hemoglobin 37 per cent (5.7 Gm.); white blood cell count 5,300; platelets 44,000; color index 0.9.

Marrow examination. The marrow was hypercellular. Megakaryocytes were increased; granulopoiesis was orderly; erythropoiesis was normoblastic and increased. Large aggregates of lymphocytes were observed.

The finding of large islands of lymphocytes was considered diagnostic of chronic lymphocytic leukemia. The profound anemia and thrombocytopenia, and severe leukopenia were undoubtedly secondary to a hypersplenic effect of the involved spleen. Whether this was a factor in the etiology of the anemia was investigated. Splenectomy for symptomatic relief of the thrombocytopenia and granulopenia was advised.

Hemograms. Just before clamping the splenic artery, the platelet count was 9,000, and the reticulocytes, 2.4 per cent. The red blood cell count was 3.53 million after preoperative transfusions, and white blood cell count, 4,650. Fifteen minutes after the splenic artery was

clamped, the platelets rose to 18,000, and the white blood cells to 6,550; the red blood cells fell to 3.39 million. Two hours after splenectomy, platelets numbered 128,000, reticulocytes 1.8 per cent, white blood cells 17,550, and red blood cells 4.5 million.

Diagnosis. A diagnosis of chronic lymphocytic leukemia with hypersplenism was made, and a good symptomatic response followed splenectomy. The spleen showed changes compatible with the diagnosis of chronic lymphocytic leukemia.

Case 2

A. H., a white woman, aged 87, was disoriented when admitted. Weakness had been progressive. The patient had been treated with liver extract, presumably for pernicious anemia.

Physical examination. There was evidence of weight loss. Pallor and a smooth, red tongue were noted. The liver was enlarged 2 cm. below the costal margin, and the spleen, which was firm, was enlarged 12 cm. below.

Hemogram. The hemogram read: red blood cells 2.03 million, hemoglobin 36 per cent (5.6 Gm.), white blood cells, 2,750 (granulocytes 1,265), platelets 150,000, reticulocytes 7.7 per cent, color index 0.9; red blood cell fragility 0.50 per cent to 0.36 per cent, cold agglutinins 1:256, and the result of Coomb's test, 4 plus.

Marrow. The marrow was hypercellular. Megakaryocytes were present and appeared normal. The nucleated red cell to white cell ratio was approximately 3 to 1. Erythropoiesis was normoblastic; granulopoiesis was intact.

Diagnosis and treatment. A diagnosis of acquired hemolytic anemia with leukopenia due to hypersplenism was made. Splenectomy was advised and accomplished successfully.

The spleen exhibited congestion of the sinusoids and reticulo-endothelial hyperplasia.

Case 3

T. T., a white woman, aged 67, was admitted because of weakness, anorexia, and weight loss of six months' duration. Severe crippling rheumatoid arthritis had been progressive for years, during which time the patient had been treated with liver extract, vitamins and iron.

Physical examination. The patient was pale, her joints were deformed, and there was evidence of weight loss. A systolic apical murmur was heard. The liver was enlarged 4 cm. below the costal margin and the spleen was enormously enlarged. (A few white and red blood cells and hyaline casts were reported on urinalysis.)

Hemogram. The pertinent features of the hemogram were: red blood cell count 3.28 million, hemoglobin 8.1 Gm., white blood cells, 2,300 (granulocytes 1,334), platelets 15,000 and color index 0.7.

Marrow. The marrow was hypercellular. Megakaryocytes were numerous, and many were young. The nucleated red cell to white cell ratio was about 1 to 2. There was a shift to the left in both granulopoiesis and erythropoiesis.

Diagnosis. The diagnosis was hypersplenism with severe pancytopenia. Splenectomy was advised. The etiology of the splenomegaly was undetermined.

Splenectomy resulted in a complete restitution of hematologic values (hemoglobin 14 Gm., red blood cells 5.2 million, granulocytes 5,460, and platelets 200,000), but there was no explanation of the huge spleen even after examination of the sections, which revealed only congestion and reticulo-endothelial proliferation.

Case 4

E. U., a white woman, aged 67, was admitted because of vaginal bleeding of six weeks' duration. The patient gave a five-year history of "black and blue" spots. Liver extract had been administered over the same period. Splenomegaly had been known to be present for twenty-five years.

Liver and spleen. The liver was enlarged 6 cm. below the costal margin and the spleen was enormously enlarged, filling more than the left half of the abdominal cavity.

Hemogram. The red blood cell count was 4.60 million, hemoglobin 85 per cent (13.2 Gm.), white blood cell count, 6,000, platelets 30,000, and color index 0.9.

Marrow. The marrow was hypercellular. Megakaryocytes were numerous but many were young. The nucleated red cell to white cell ratio was about 1 to 1. Both erythropoiesis and granulopoiesis were normal. Gaucher's cells were present in large numbers throughout the marrow substance.

Diagnosis. A diagnosis of Gaucher's disease was made. Thrombocytopenia was thought to be on the basis of hypersplenism resulting from the involvement of the spleen by Gaucher's disease.

Splenectomy was recommended and performed. There was an immediate rise in the level of the platelets. The spleen was extensively involved by Gaucher's disease.

Case 5

B. P., a white woman, aged 59, was under observation since the age of 50 for weakness, granulopenia, anemia, variable thrombopenia and splenomegaly. The first marrow examination revealed a remarkable infiltration of lymphocytes. A presumptive diagnosis of chronic lymphocytic leukemia or lymphosarcoma was made. Subsequent transfusions and splenic irradiation were of only temporary value in correcting anemia and neutropenia (from 950 to 1,750). The clinical course was complicated by several respiratory infections. Splenectomy was recommended.

Prior to splenectomy physical examination revealed obesity, and splenomegaly; the spleen was 2 cm. below the left costal margin.

Hemogram. The hemogram read: hemoglobin 55 per cent (8.65 Gm.), red blood cell count 2.76 million, color index 1.0, white blood cell count 4,100 (granulocytes 2,850), and platelets normal. A lupus erythematosus preparation yielded negative results.

Marrow. The marrow was normocellular. Megakaryocytes were present in normal numbers. The nucleated red cell to white cell ratio was approximately 1 to 1, denoting an increase in erythropoiesis. Erythropoiesis was normoblastic. Granulopoiesis was decreased. Mature and young lymphocytes were moderately increased.

Diagnosis and treatment. A diagnosis of probable lymphosarcoma of the spleen with secondary hypersplenism was made.

Removal of a fibrocongestive spleen weighing 390 Gm. was followed by a rise in hemoglobin to 78 per cent (12.2 Gm.), but little change in the granulocyte count (3,000).

Case 6

F. K., a white woman, aged 63, was examined because of infected ulceration of the hands, which had been present for six or seven years, and because of more recent ulcerations of the left breast and axilla.

Physical examination. Indolent ulcerations were present but the spleen could not be palpated. Roentgenographic examination of the abdomen disclosed splenomegaly.

Hemogram. Hemoglobin 67 per cent (10.5 Gm.), red blood cell count 3.9 million, color index 0.9, white blood cell count 1,100 (granulocytes 640), and platelets normal.

Marrow. The marrow was hypercellular, with normal megakaryocytes. The nucleated red cell to white cell ratio was 1 to 2, denoting increased erythropoiesis. Erythropoiesis was normoblastic. Granulopoiesis was increased and showed a shift to the left. Lymphocytes were increased.

Diagnosis and treatment. The diagnosis was splenomegaly of unknown cause, with anemia and granulocytopenia due to hypersplenism. At the time of splenectomy the spleen weighed 460 Gm. Histologic examination showed congestion. Healing of all ulcerations followed as the hemoglobin rose to 82 per cent (12.8 Gm.) and the granulocyte count to 6,300.

SUMMARY AND COMMENT

1. Hypersplenism is a vague and poorly understood term, which nonetheless allows a working designation for a group of conditions characterized by various

cytopenias, splenomegaly, and qualitatively and quantitatively adequate normal marrow.

2. Hypersplenism should be considered in all cases of splenomegaly.

3. When the diagnostic criteria are satisfied, splenectomy should be performed.

4. The success of splenectomy in the 6 illustrative cases reported clearly demonstrates the practical importance of recognizing the hypersplenic syndrome of (a) paucity of erythrocytes, granulocytes and thrombocytes in the blood—any one or any combination may be deficient; (b) increased normal precursors in the marrow, of cellular elements deficient in the blood; and (c) enlargement of the spleen. Symptoms attributable to hypersplenic anemia and granulocytopenia constitute precise indications for splenectomy; the bleeding of hypersplenic thrombocytopenia presents the most urgent indication, particularly in the aged patient in whom degenerative vascular changes increase the likelihood of fatal hemorrhage.

5. In all cases, meticulous preoperative preparation and postoperative care are essential. Blood transfusions, cortisone, ACTH, antibiotics, and early ambulation should be utilized judiciously.

6. The immediate prognosis in hypersplenism following splenectomy is usually good, but the ultimate prognosis depends on the underlying disease, for the underlying disease is not affected by splenectomy. In view of this, hypersplenism is arbitrarily divided into two groups—primary, when the splenic enlargement is an isolated finding; and secondary, when it is part of a systemic disease. The incidence of cure by splenectomy is 80 per cent in primary hypersplenism, but this operation provides only symptomatic relief in secondary hypersplenism. The eventual development of a blood dyscrasia in the primary group is always a possibility.

7. The mortality rate in splenectomy for primary hypersplenism is about 1 per cent, and for secondary hypersplenism about 5 per cent, because of the associated systemic disease.

HOST-TUMOR ANTAGONISM.

IV. Immunologic Possibilities Inherent in Some of the Theories on the Nature of Cancer

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I. INTRODUCTION

It has been known for half a century that a spontaneous tumor arising in an animal can be successfully transplanted to many other animals of the same species, but not to all. In the unsuccessful cases, it became extremely important to find the nature of this immunity, if it actually existed. Woglom (1) reviewed the evidence and came to the conclusion that it was not possible in animals of pure strains to induce resistance to tumors originating within their own strain. The degree of resistance induced varied directly with the genetic interrelationship of the host and the tumor and the donor of the blood used for experimental immunization. (The donor of the blood in such an instance would be an animal of the same species in which, for some reason, the tumor had regressed.) Thus immunization appeared ineffective against tumors of animals of the same genetic constitution as the host of the primary tumor. If no genetic difference existed between the tumor and the host, there was no basis for immunization. Such was the status of this problem until very recent times.

Recently, Lewis and Aptekman (2) were able to induce resistance in inbred rats against a tumor that normally results in practically 100 per cent successful transplantation. They immunized rats against a subsequent challenge injection of the tumor by one of two methods—either by a previous injection of an alcoholic extract of the tumor or by strangulation of a growing tumor with subsequent spontaneous absorption of the necrotized neoplasm. The strangulation could be induced by sewing the neoplasm into a pocket and obliterating the blood vessels, or by injecting epinephrine into the tumor. The induced resistance to a subsequent challenge injection of the tumor appeared to be permanent.

Now that the possibility of inducing resistance to a neoplasm in the same strain of animal as the original host seems to be realized, it was thought to be of interest to re-examine some of the theories on the nature of cancer (3) and explore some of the immunologic concepts.

II. THEORIES OF THE CAUSATION OF CANCER

1. The oldest theory is that the tumor originates from misplaced embryonal cell rests. Since a tumor in any organ is possible, one would have to assume such cell groups lying dormant in all tissues. It would not explain the occurrence of occupational tumors in man, or tumors caused by cancer-inducing

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chemicals in animals. It could not explain the conversion of normal cells to cancer cells in tissue culture. No immunologic possibilities are inherent in this theory.

2. Another theory is that the tumor cell has been parasitized by a virus, which by its presence constantly stimulates cell multiplication. A virus has been found as the cause of many tumors in animals, but it has never been proved for true neoplasms in human subjects. According to this concept, in the human neoplasm a virus causes a self-perpetuating combination with the chromatin of the cell nucleus, and the continuing presence of the virus is considered no longer necessary. Once the new anabolic processes are set up, they cannot be regulated by the body.

This theory cannot explain the great variation in types of cancers all over the universe, unless it be assumed that the causative virus of each type of tumor is present everywhere. Immunity to virus diseases is frequently observed, but why is immunity so rare in cases of carcinoma, if actually caused by a virus?

3. The important mutation theory holds that a transmissible metabolic abnormality is initiated by somatic cell mutation rather than by virus causation. Although this theory explains many experimental findings which will be detailed later, it cannot completely explain certain important facts. Some of the carcinogens are not mutagenic to cells. A somatic mutation would not necessarily set off a chain of continuous cell proliferations, since it may occur in resting somatic cells. The theory cannot explain why the cell proliferation is not associated with differentiation, organization, and the assumption of special functions, such as occur in normal cells. A mutation in germ cells may change the physical features in the mutant, but does not change the quantity of cells as in cancer. It has been stated the neoplasia is associated with the change of a few genes. Actually in microscopic sections of cancer, the chromatin in the nucleus is markedly abnormal, so that most of the genes in the chromosome probably are abnormal.

There is some important work, however, that fits rather well with the theory of cancer as a somatic mutation. Furth, Boon and Kaliss (4) state, "The transplantation pattern of normal tissues of inbred mice thus far studied is monotonously uniform in mice of pure lines and in known hybrids. The transplantation pattern of leukemias and tumors arising in the same inbred stocks may differ greatly from that of normal tissue. Induced leukemias and tumors may differ greatly among themselves, but there is a transplantation pattern characteristic of each neoplasm, and this is retained through numerous passages. If differences in transplantation pattern are based on genic differences, then this abrupt, discontinuous and irreversible change is not an abnormal differentiation but a somatic mutation. The causes of cancers are complex and viruses doubtless are prominent among them, but the immediate change that makes some cells cancerous in the course of chemical carcinogenesis may be a somatic mutation."

Earlier, Furth and Barnes (5) studied the transplantation relation of cells from leukemias in A.K. and R.F. inbred stocks. They showed that transplanta-

tion patterns of neoplastic blood cells from several leukemias induced in the same inbred stocks may differ among themselves and from that of spontaneous leukemias. For example, leukemias arising in the F_1 or F_2 hybrids could be grafted to mice of both parental stocks or to mice of neither stock, though they were readily transplantable to hybrids, or they could be transplanted to only one of the parental stocks. The authors interpreted these differences as supporting the hypothesis that the cells of the induced leukemias are genetic mutants.

MacDowell, Potter *et al.* (6) induced active resistance to experimental leukemias in mice by means of sublethal doses of living leukemic cells. This resistance could be passively transferred to suceptible mice by the use of saline suspension of minced tissues from actively immunized animals. Genetically identical living cells from nonimmunized mice provided no protection.

MacDowell, Potter and Taylor (7) found that the C58 inbred strain of mice which had a spontaneous leukemia rate of about 90 per cent could be immunized against the highly virulent cells of a long established line of transplanted leukemia. This leukemia had started from a spontaneous tumor in a mouse of the same inbred strain. The authors interpreted this result as meaning that the induced resistance to highly virulent long-transplanted leukemia cells depends on properties developed in the course of transplantations, that is, the development of a mutation.

Barrett (8), using differential sedimentation with chicken tumor I, observed a demonstrable immunologic difference between extracts of chicken tumor and similar material from normal tissues. This is suggestive evidence that the tumor cells are mutants of similar normal cells.

Dunning and Curtis (9), working with a transplantable malignant hepatoma induced by 2-acetylaminofluorene in the liver of a rat, grew it progressively in 100 per cent of the inoculated rats of the same inbred strain in the first seven transfer generations. In later transfers, some of the rats of the same line had a regression of the transplanted tumor and were resistant to all subsequent inoculations with it. More female than male rats acquired this immunity. The resistant rats occurred at random in different litters from many matings and could not be attributed to a single mutation. The ability to acquire the resistance was not markedly enhanced by previous regression of another transplanted tumor or by intraperitoneal injection of serum obtained from rats that had acquired the immunity. Nevertheless, the best explanation of this transplantation immunity is the development of a mutation in the tumor in the later transfer generations; since genetic differences would then exist between tumor and host, immunity could be induced.

4. Certain chemical theories have been proposed for the origin of cancer, but they seem to be a combination of the virus and mutation theories. One of the most recent indicates an essential difference in purine and pyrimidine requirements between the normal and neoplastic cells. This finding may be a result rather than a cause of the neoplasm.

5. An interesting recent theory is that cancer results from an artificial parthenogenesis of somatic cells (3). All of the theories previously mentioned fail

to explain the cell multiplication, and why the body cannot stop the process. According to the concept enunciated by Steiner (3), a neoplasm represents a growth of somatic cells initiated by a parthenogenetic stimulus, but the body has no mechanism to stop the abnormal gestation, and it continues to grow. A tumor can be likened to a highly pathologic pregnancy—but it arises from somatic cells rather than germ cells, and it is not initiated by fertilization of ova by sperm cells but by activation of cells by diverse chemical and physical agents. The host has no physiologic mechanism of disposing of the fetus. The frequency of cells showing chromosomal disturbances is similar in parthogenetically stimulated ova to that found in cancer. No two tumors are ever identical in behavior or morphology. Somatic cells also have different inherent potentialities. Steiner mentions that the mature cell types so greatly resemble an abnormal fetus that the suggestion has been made that they arise from parthogenetic development of an ovum. In line with this theory, these tumors may arise from somatic cells that have multiple potentialities. Chronic irritation as a causative factor fits in well with the parthogenetic theory. The list of carcinogenic agents seems to resemble closely that of the known parthenogenic agents. According to this theory, control is theoretically possible by withholding the etiologic agents and increasing cell resistance; and cure, by destroying or removing the abnormal cells, by withholding their nutrition, by reversing the key abnormality, or by increasing host resistance to the autoparasite.

Professor Hadfield (10), commenting on the phenomenon of long survival in cancer patients, speaks of the "dormant cancer cell" that may remain inactive for a shorter or longer time, and then become active once more. He likens this phenomenon to cancer cells becoming inactive when exposed to low temperatures and then becoming active again and causing neoplasms on implantation. Kennaway (11) in searching for another similar phenomenon in nature (*i.e.*, a dormant state of cells under normal conditions), mentions "delayed implantation of certain mammalian species."

Delayed implantation is found in many species, such as the European badger and the American martin. Fertilization takes place in July or August, the egg develops for a few days, and then lies dormant in the blastocyst stage until January, when it is implanted. Development then proceeds normally, and birth is in March. The dormant period can be made three months shorter by exposing the pregnant females to artificial light during the winter months, which suggests that the pituitary gland may be involved.

This information fits in well with the theory that likens a tumor to a parthogenetically induced conception of somatic cells, and perhaps may explain one phase of the discontinuous growth noted in some cancers.

III. DISCUSSION

Before discussing some of the recent literature on the subject, delineation of a few simple terms may be in order:

1. Autologous: referring to grafting of a tissue or tumor occurring naturally in the individual.

2. Homologous: referring to tissue or tumor from another animal of the same species.

3. Heterologous: referring to a tumor or tissue from an animal of another species.

Much of the recent work applicable to tumor transplantation has been in the field of normal tissue transplantation, *i.e.*, homologous skin grafting or skin homografting. The principles evolved by this technique have been shown to be valid in organ transplantation and also in tumor transplantation.

There is very little difference between a skin homograft and a skin autograft in the early stages. A skin homograft has every clinical and microscopic indication of survival initially. Blood can be seen to circulate as freely in the homograft as in the autograft. Yet after about a week of survival, thromboses occur in the blood vessels connecting the homograft to the host bed; this results in the death of the graft, and its rejection (12). There is an overwhelming body of evidence that the reason for the death and rejection of the homograft is an actively acquired immunity in the host in response to the presence of the homograft. Gorer (13) has presented evidence to show that skin homografts in man stimulate antibodies that react with human red cells.

Extreme interest has centered on ways of modifying these immunologic reactions. Billingham, Brent and Medawar (14) showed that if mice were given living cells during fetal life, they did not reject skin homografts from the donor of the cells. However, skin homografts from other donors were promptly rejected. The retention of homografts by the device of exposure to donor cells in utero has been called acquired tolerance. Others have shown that acquired tolerance can be induced by implanting cells of the prospective donor on the first day of life (15). This procedure can also be used to induce acquired tolerance to purified protein antigens, if these are given on the first day of life.

In mature animals, a state called immunologic paralysis can be induced by large quantities of the antigen, after which the animals lose their power to form antibodies to this specific antigen (16). It is felt that similar immunologic mechanisms underlie the phenomena of acquired tolerance and immunologic paralysis.

Extremely important for our thesis is the fact that Kaliss and Snell (17) have shown that it is possible to induce immunologic paralysis to tumor transplants in previously resistant animals by using large amounts of lyophilized or fresh tumor. Even more interesting is the fact that tolerance can be abolished, or transplantation immunity can be again induced in the animal.

It was shown by Mitchison (18) that heightened resistance to a strain-specific mouse tumor homograft could be passively conferred upon a normal host of some other strain by grafting into it the regional lymph nodes of a member of the host's strain which had been actively immunized against the tumor. The actual effect of this procedure is to make the recipient of the immune lymph nodes behave toward a tumor homograft exactly as if it had been actively immunized itself. It is not a passive immunization, but an active immunization by proxy. Billingham *et al.* (19) demonstrated this principle as follows: If a

skin homograft from an A-line mouse is tolerated (acquired tolerance method) by a CBA host, the graft can be promptly destroyed by an intraperitoneal inoculation of the tolerant host with fragments of the regional lymph nodes excised from normal CBA mice which have reacted against and rejected grafts of A-line skin. Thus a tolerated graft that has survived in an autograft-like state for at least seventy-five days begins to deteriorate visibly in three or four days after inoculation of the host with "immune" nodes and is rejected by necrosis and scabbing nine to fifteen days after inoculation. In an alternate experiment in which the regional lymph nodes of a normal CBA mouse are implanted into a tolerant CBA mouse, visible deterioration of the graft also occurs, but at a slower rate.

Billingham *et al.* (19) feel that these experiments show that tolerance of a homograft is attributable to a central failure of the host's mechanism of immunologic response. The tolerated graft continues to be vulnerable to an immunity reaction induced against it.

Tolerance can be reversed by other tissues also. For example, Chase (20) has shown that hypersensitivity can be transferred from a sensitive to a nonsensitive animal by way of intact transferred leukocytes. Transfer of transplantation immunity to tumors or skin homografts has also been demonstrated by means of transferred leukocytes and, as noted, by immune lymph nodes.

There is a congenital human disease, agammaglobulinemia, which is probably the natural analogue of immune paralysis in the animal. These patients accept skin homografts from genetically unrelated donors (21).

Smith and Good (21) submit the intriguing possibility, based on the foregoing work, that an understanding of the capacity of the human patient with cancer to acquire tolerance for his malignant cells may suggest techniques for inducing transplantation immunity or reversing the tolerance. Thus if a malignant neoplasm may be considered as a genetically related homograft, or as a homograft in a patient with immunologic paralysis, then transplantation immunity to the tumor could be induced in a genetically unrelated host. This immunity could then be transferred to the patient by means of leukocytes or regional lymph nodes, conceivably resulting in rejection of the homotransplant and lysis of the tumor. This is a remarkable possibility, and it seems to be entirely logical.

REFERENCES

1. Woglom, W. H.: Immunity to transplantable tumors, *Cancer Review* **4:** 129, 1929.
2. Lewis, M. R., and Aptekman, P. M.: Atrophy of tumors caused by strangulation and accompanied by development of tumor immunity in rats, *Cancer* **5:** 411, 1952.
3. Steiner, P. E.: The nature of cancer, *in* Proc. of First Canadian Cancer Research Conference, ed. by R. W. Begg. New York, Academic Press Inc., 1955.
4. Furth, J.; Boon, M. C., and Kaliss, N.: On the genetic character of neoplastic cells as determined in transplantation experiments, *Cancer Research* **4:** 1, 1944.
5. Furth, J., and Barnes, W. A.: Difference between malignant blood cells from induced and spontaneous leukemias of mice, *Cancer Research* **1:** 17, 1941.
6. MacDowell, E. C.; Potter, J. S., and others: Experimental leukemia, *Carnegie Inst. Washington Yearbook* **37:** 47, 1938.

7. MacDowell, E. C.; Potter, J. S., and Taylor, J. J.: Influence of transplantation upon immunological properties of leukemia cells, *Proc. Nat. Acad. Sc.* **25:** 416, 1939.
8. Barrett, M. K.: Influence of genetic constitution upon induction of resistance to transplantable mouse tumors, *J. Nat. Cancer Inst.* **1:** 387, 1940.
Barrett, M. K.: The antigenic nature of purified chicken tumor agent, *Cancer Research* **1:** 543, 1941.
9. Dunning, W. F., and Curtis, M. R.: Spontaneous regression conferring permanent immunity to a transplantable malignant hepatoma in rats of an inbred line and attempts to transfer the immunity to other rats of the same line, *Caryologia* (Suppl.) **6:** 639, 1954.
10. Hadfield, G.: The dormant cancer cell (Kettle Memorial Lecture), *Brit. M. J.* **2:** 607, 1954.
11. Kennaway, E. L.: The dormant cancer cell (Letter) *Brit. M. J.* **2:** 1225, 1954.
12. Converse, J. M., and Rogers, B. O.: Introduction: relation of immunology to tissue homotransplantation, *Ann. New York Acad. Sc.* **59:** 279, 1955.
13. Gorer, P. A.: The antibody response to skin homografts in mice, *Ann. New York Acad. Sc.* **59:** 365, 1955.
14. Billingham, R. E.; Brent, L., and Medawar, P. B.: Actively acquired tolerance of foreign cells, *Nature* **172:** 603, 1953.
15. Billingham, R. E., and Medawar, P. B.: "Desensitization" to skin homografts by injections of donor skin extracts, *Ann. Surg.* **137:** 444, 1953.
16. Felton, L. D.: The significance of antigen in normal tissues, *J. Immunol.* **61:** 107, 1953.
17. Kaliss, N., and Snell, G. D.: The effects of injections of lyophilized normal and neoplastic mouse tissues on the growth of tumor homoiotransplants in mice, *Cancer Research* **11:** 122, 1951.
18. Mitchison, N. A.: Passive transfer of transplantation immunity, *Nature* **171:** 267, 1953.
Mitchison, N. A.: Passive transfer of transplantation immunity, *Proc. Roy. Soc., London*, Series B, **142:** 72, 1954.
19. Billingham, R. E.: Brent, L., and Medawar, P. B.: Acquired tolerance to skin homografts, *Ann. New York Acad. Sc.* **59:** 409, 1955.
20. Chase, M. W.: The cellular transfer of hypersensitivity to tuberculin, *Proc. Soc. Exper. Biol. & Med.* **59:** 134, 1945.
21. Smith, R. T., and Good, R. A.: Some new horizons for clinical medicine, *Univ. Minnesota Med. Bull.* **27:** 96, 1955.

ANTICHOLINERGICS IN THE MANAGEMENT OF PEPTIC ULCER IN THE GERIATRIC PATIENT, WITH SPECIAL REFERENCE TO THE DANGER OF URINARY RETENTION AND GLAUCOMA

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PEPTIC ULCER

It has been frequently suggested that gastroduodenal (peptic) ulcer is uncommon in the aged, that its peak incidence is in patients between 30 and 40 years of age, and that when symptoms are first manifested in the sixth decade, malignancy should immediately be considered. These statements may have been more accurate several years ago, when diagnostic techniques were not as well developed as today and when the percentage of the population in the sixth decade was much lower than at present.

Incidence. The age distribution of the white population of the United States shows slightly more than 10 per cent over the age of 60. When the incidence of gastroduodenal (peptic) ulcer is examined in relation to the percentage of the population aged 60 and over, it is apparent that it equals the incidence in younger age groups. In a study of 4,079 cases of peptic ulcer collected from the literature, Mulsow (1) found an incidence of 10.5 per cent in persons over the age of 60—coinciding with the percentage of the population in this age group. Thus peptic ulcer was as common after the age of 60 as in younger persons. A similar age-ulcer relationship was noted by White (2) in a study of 934 private patients. It can therefore be predicted that with the increase of life expectancy in the adult population, there will be an increase in the occurrence of benign gastroduodenal ulcer proportionate to the increase in the percentage of our population over the age of 60.

Diagnosis. It is likely that cases of peptic ulcer in older people do not appear as frequently in statistics as they should. A large group of patients who have had recurring peptic ulcer for many years, and have learned personally to manage the disease by means of diet and alkalies, do not present themselves for medical management. Since many of the aged have a subnormal response to discomfort and pain, the symptoms of ulcer are non-characteristic. Moreover, the frequency of vague digestive complaints secondary to many degenerative diseases, tends to increase the confusion. The lack of severe distress, the bizarre nature of the symptoms, and the frequency of other disease which may give rise to similar symptoms, often delay proper investigation and the correct diagnosis is not established. Since most of these ulcers have a marked tendency

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towards healing, a remission may occur, and the diagnosis of peptic ulcer is never recorded.

The mortality rate in benign gastroduodenal ulcer increases after the age of 50, primarily due to the higher incidence of chronicity with its attending complications. The increasing incidence of cardiovascular disease in association with the aging process makes the risk of surgery greater, and markedly increases the mortality rate from hemorrhage.

MEDICAL MANAGEMENT

Not only does the geriatric ulcer patient present a peculiar problem in diagnosis but the usual therapeutic regimen cannot always be applied in the same routine-like fashion as in younger individuals.

Diet

Dietary management may be complicated by several factors. Frequently coincidental disease requires a modification of the usual ulcer diet. Caloric content and sodium content may have to be carefully estimated in the cardiac or hypertensive peptic-ulcer patient. Habit patterns are extremely rigid, and changes in the nature and frequency of food intake are often resisted. Many older people have peculiar dietary habits, *e.g.*, coffee and rolls for breakfast and for lunch, and one major meal in the evening. Food prejudices are firmly entrenched and it is frequently impossible to convince the patient that those foods he considers to be constipating, laxative, easy to digest, or hard to digest, are anything other than what he believes them to be. Difficulty in mastication due to lack of properly fitted dentures is a factor which calls for correction.

Alkalies

Neutralization therapy by means of alkalies no longer presents the threat of alkalosis, as long as the nonabsorbable alkalies are utilized; nor need there be the former special concern about the adequacy of the patient's renal function. These nonabsorbable alkalies, however, do have an effect on the large intestine and their irritating or constipating effect still presents a problem and further complicates management.

Anticholinergics

Anticholinergics of the newer synthetic variety have largely replaced traditional belladonna and belladonna alkaloids in the ulcer regimen. Most of the anticholinergics, however, when used in physiologically effective doses, have an atropine-like effect on other organs. In a geriatric patient these physiologic side-effects can be not only distressing, but at times dangerous.

Constipation. Most patients are already consuming laxatives of one type or another with great regularity or using enemata at frequent intervals. This tendency towards constipation, when aggravated by the antispasmodic effect of another drug on the large intestine, is very disturbing to the patient, particularly as he already is greatly concerned about his bowel function.

Xerostomia. It has commonly been our practice when using atropine in the management of peptic ulcer, to increase the dosage until the patient exhibits constant dryness of the mouth but has no loss of pupillary accommodation. In younger subjects, this method of therapy is used by many physicians. In obtaining the full physiologic effect of atropine, the response to therapy is enhanced. In older persons the frequent presence of artificial dentures creates great distress during drug-induced xerostomia. One may have to choose between obtaining a modified effect from the drug or disturbing the patient so much as to make him uncooperative.

Urinary retention. It is now accepted routine in the management of peptic ulcer in elderly men to inquire carefully into urinary function. The presence of marked nocturia, slowing of the stream, or any other evidence of prostatic hypertrophy with bladder-neck obstruction contraindicates the use of large doses of anticholinergics. In some of these patients, even small doses will produce relaxation of the detrusor of the bladder and consequent complete urinary retention. In the experience of most physicians using the newer anticholinergics, an emergency call to catheterize the patient often becomes necessary. Although the occurrence of complete urinary retention is distressing and inconvenient to the physician, the damage is usually not irreparable. Following cessation of the drug, there is prompt restoration of normal function.

Glaucoma. A more serious and frequent side-effect of parasympatholytic drugs is the aggravation of an existing tendency towards glaucoma. It is estimated that 1 person in 40 over the age of 40 has undiagnosed compensated glaucoma. Lemoine (3), in a review of 816 patients with 1,112 glaucomatous eyes, reported an incidence of 85 per cent in patients over the age of 45 years. Berens and Nilson (4), in a study of 53 cases of unselected patients with compensated glaucoma, noted that more than half were between the ages of 40 and 70. Frequent warnings have been issued to use care in the systemic administration of atropine and other drugs of similar action in patients over the age of 45. Ullman and Mossman (5) studied 25 cases of primary glaucoma. Approximately 25 per cent were aggravated or induced by the internal application of belladonna; and in 5 out of 6 of these, the patients were over the age of 60. Larmande and Toulant (6) echoed their plea for greater care in the administration of these drugs in the older age groups.

The onset of increased intraocular tension is not attended by marked symptoms. It may, therefore, advance to a status of irreparable damage to the retina. It is not necessary to destroy the powers of accommodation in order to produce decreased drainage and precipitate a damaging episode of increased intraocular tension or glaucoma. The forewarned patient who experiences even moderate loss of accommodation will promptly report it to his physician. If, however, accommodation is not markedly affected, the patient may continue on his way consuming his drugs while intraocular tension increases. On occasion, this increased intraocular tension will cause headache and, reflexly, further gastro-intestinal symptoms. Unfortunately, these symptoms are sometimes interpreted as an inadequate response to therapy, and the dose of the

drug is increased, thereby perpetuating a vicious cycle. One ophthalmologist reported to me that among his first questions to an older person complaining of blurring of vision is, "Do you have any stomach trouble?" In a large percentage of patients he finds evidence of digestive symptoms and a record of therapy with belladonna or one of the synthetic anticholinergics. Since glaucoma is an important cause of blindness in this country today, a simplified tenometer should be included in the armamentarium of every physician practicing geriatric medicine. (The tenometer used in this study is highly recommended.)

CLINICAL STUDY OF EFFECT OF A SYNTHETIC ANTICHOLINERGIC (PIPTAL) IN PEPTIC ULCER

In the search for an effective anticholinergic devoid of inconvenient or dangerous side-effects in the older age groups, the following study was undertaken with what appeared to be a promising drug. N-ethyl-3-piperidyl-benzilate methobromide (Piptal®)[1] in preliminary studies (7, 8) had been shown to possess marked parasympatholytic activity. Its pharmacodynamic action appeared to be that of a specific postganglionic parasympathetic depressant. Clinical studies indicated (9, 10) a good spasmolytic effect on the stomach, with depression of gastric secretory activity. Effects such as constipation and urinary suppression appeared to be negligible.

Method

In order to measure the effectiveness of the drug under investigation in relation to the presence or absence of side-effects, objective methods were utilized wherever possible.

Urinary flow was measured with a flow-meter which records the volume of urine on a moving chart having an abscissa which represents the time in seconds.[2] The machine does not require the presence of an operator during use. Therefore all psychologic factors induced by the presence of a second party are removed. The first flow of urine activates an electrical switch which starts the constant-speed motor. The pen records a graph representing the urinary flow on a volume-time basis. After the bladder has been emptied, the instrument may be allowed to continue running until the operator returns to the room. He then closes the switch and resets the machine for the next patient. Prolonged trial (11) has established the normal rate for adult men exceeds 16 cc. per second during the period of greatest flow. This period of greatest flow can be determined by comparing the slope of any portion of the graph with that of a standard. It is also possible to plot different rates of flow on the graph itself. If the graph does not present a slope exceeding 16 cc. per second with a bladder containing 200 cc. or more of urine, the flow is abnormally slow, usually due to obstruction of the bladder neck or weakness of the detrusor. All graphs obtained in association with a volume of urine of less than 200 cc. were discarded. Readings were taken prior to the administration of the drug and then during the course of therapy, at stated intervals.

Intraocular tension was measured by the Berens-Tolman ocular hypertension indicator. This is a simplified but accurate instrument, designed for the physician who does not have special ophthalmologic training. It records only 3 measurements—normal, subnormal or

[1] Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

[2] Charles Meriam Co., Los Angeles, Calif.

increased intraocular tension. Readings were taken on all patients prior to, and repeatedly during, the administration of the drug. If the reading at any time was in the increased range, the patient was re-examined by a qualified ophthalmologist.

Constipation and xerostomia, were primarily estimated by patient interview, since no objective method was available. The effect of the drug on constipation was difficult to evaluate because of the change in dietary habits and because some effect could be attributed to alkali therapy. The patient was otherwise questioned as to the ease and frequency of bowel movements prior to, and during the course of treatment.

The patient was questioned directly concerning mouth dryness, and with regard to blurring of vision during reading.

Material

The 32 subjects of the study had records of either duodenal, gastric or stomal ulcers which produced symptoms severe enough to cause them to apply for medical care. Since urinary side-effects are most distressing in male patients, the group consisted only of men. They were all members of the Pacific Electric Railway Hospital Association, including several retired employees. Although information was collected on a much larger series of patients, only the 32 in whom the data were complete were used in this study. The average age of this group was 53 years.

The usual dosage of Piptal was 5 mg. four times daily, increased to 10 mg. per dose when required.

Results

The ages of the patients according to decades are listed in Table 1. The unusually large group aged 60 and over (10 men) was due to the large proportion of retired employees.

The clinical effects of Piptal are listed in Table 2.

Intraocular tension. Only 2 of the 32 patients (Table 2) exhibited increased intraocular tension. R. S., aged 41, was found to have increased tension in the left eye prior to the administration of Piptal, but during treatment with a dosage of 10 mg. four times a day, the tension in the left eye returned to normal. In F. V., aged 59, increased intraocular tension in both eyes developed after administration of Piptal. The drug was stopped and the tension returned to normal; re-institution of therapy did not produce another rise. The dosage was increased to 10 mg. four times a day, but repeated examination failed to reveal any effect upon intraocular tension. It was concluded that these 2 patients

TABLE 1

Age Distribution

Age	No. of Cases
20–29	2
30–39	2
40–49	10
50–59	8
60–69	9
70–79	1
Total	32

TABLE 2

Effect of Piptal in 32 Men with Peptic Ulcer*

Patient	(Age (yrs.)	Type of Ulcer	Maximum rate of Urinary Flow (cc./min.)		Intraocular Tension		Piptal Therapy (mg. q.i.d.)	Relief of Ulcer Symptoms	Side-effects
			Before	After	Before	After			
1. A. E. B.	60	Duodenal	10	10	N†	N	5	Good	None
2. E. F. C.	47	Duodenal	35	35	N	N	10	Excellent	Dry mouth
3. R. B.	27	Duodenal	15	15	N	N	10	Good	None
4. C. N. B.	51	Gastric	30	30	N	N	10	Inadequate (surgery)	Dry mouth
5. A. B.	78	Duodenal	30	20	N	N	5	Excellent	None
6. E. W. B.	61	Duodenal	30	30	N	N	10	Good	Dry mouth
7. C. C.	50	Duodenal	15	30	N	N	5	Good	None
8. G. D.	45	Duodenal	30	30	N	N	5	Excellent	Dry throat
9. W. S. D.	40	Duodenal	30	20	N	N	5	Good	None
10. A. F.	58	Stomal	20	25	N	N	5	Inadequate	None
11. J. F.	59	Stomal	15	15	N	N	5	Excellent	None
12. E. N. F.	45	Duodenal	15	15	N	N	5	Good	None
13. E. C. G.	49	Stomal	15	15	N	N	5	Good	None
14. R. H.	58	Duodenal	20	20	N	N	5	Good	Dizziness
15. E. P. L.	61	Duodenal	15	15	N	N	5	Good	None
16. R. McB.	41	Duodenal	25	25	N	N	5	Excellent	None
17. H. M.	69	Duodenal	10	10	N	N	10	Good	None
18. J. R. N.	40	Duodenal	20	20	N	N	10	Excellent	Dry mouth
19. C. M.	56	Stomal	30	30	N	N	10	Inadequate (surgery)	None
20. H. L. R.	32	Duodenal	30	30	N	N	5	Excellent	None
21. T. S.	40	Duodenal	30	30	N	N	5	Excellent	None
22. R. S.	41	Duodenal	30	30	Latent glaucoma		10	Excellent	None
23. F. V.	59	Duodenal	15	15	Latent glaucoma		10	Excellent	None
24. C. W.	64	Duodenal	30	30	N	N	5	Good	None
25. E. W.	39	Duodenal	30	30	N	N	10	Excellent	None
26. H. M. Y.	66	Stomal (Ca of prostate)	10	10	N	N	5	Excellent	None
27. R. S. B.	47	Duodenal	25	25	N	N	10	Excellent	Dry mouth
28. J. O'C.	58	Duodenal	12	15	N	N	10	Excellent	None
29. R. R.	50	Duodenal	30	30	N	N	10	Excellent	None
30. A. J. G.	70	Duodenal	10	10	N	N	10	Excellent	None
31. P. M.	68	Gastric	15	15	N	N	10	Excellent	None
32. H. S.	63	Duodenal	15	15	N	N	10	Excellent	None

* Piptal® (experimental indicator, JB 323)—Lakeside Laboratories, Inc., Milwaukee, Wis.

† N = Normal range on Berens-Tolman ocular hypertension indicator.

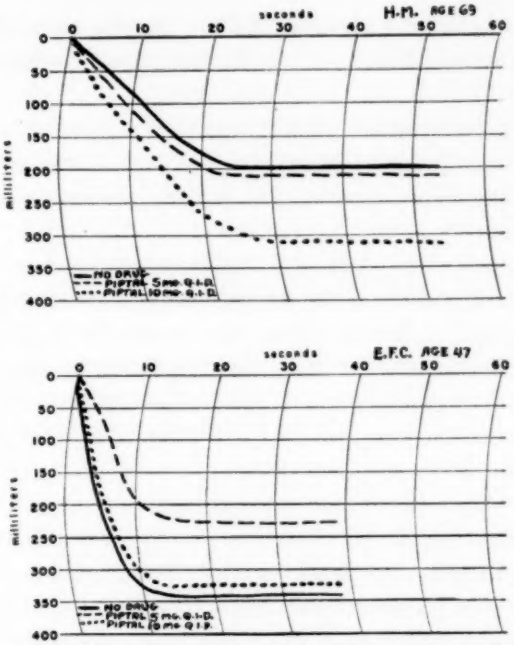

FIG. 1. The upper graph shows the effect of Piptal on urinary flow in a man with prostatic obstruction. The lower graph shows the effect of Piptal on normal urinary flow.

represented the usual incidence of compensated glaucoma, observed fairly commonly in this age group; and that the variations in intraocular tension were fortuitous. No other patients experienced changes in intraocular tension during continuous administration of the drug.

Urinary flow. Fourteen patients (Table 2) had a urinary flow of less than 16 cc. per minute with a bladder volume of more than 200 cc. of urine. All except R. B. (Case 3) were in the age group in which bladder-neck obstruction due to prostatic hypertrophy is common. In several cases there was an established diagnosis of prostatic hypertrophy and urologic therapy was being carried out; in 1 case a confirmed prostatic carcinoma was present. Eighteen patients (Table 2) had normal urinary flow.

Repeated tracings of urinary flow were made in all patients, prior to and during the administration of 5 mg. and 10 mg. of Piptal four times daily. A representative graph is shown in Figure 1. There was no evidence of decreased flow in either the normal patients or in those with prior evidence of prostatic obstruction.

Healing of ulcer. The effectiveness of the drug in the healing of benign peptic ulcers (duodenal, gastric or stomal) was estimated purely on the basis of symptomatic relief. All patients were given a bland diet with three interval feedings and all were ambulatory during the period of treatment. Alkalies were administered in adequate dosage every two hours or oftener. Piptal was prescribed in either 5-mg. or 10-mg. doses before meals and at bedtime. If the patient reported complete freedom from symptoms within one week after the institution of therapy, the results were classified as excellent. If there was complete symp-

tomatic relief after two weeks of therapy, the results were classified as good. If symptoms persisted more than two weeks, the results were classified as inadequate.

Roentgenologic demonstration of healing was not used as a measure of effectiveness of the drug because many of the lesions were chronic, with persistently deformed duodenal caps in which the demonstration of a crater was exceedingly difficult.

It has never been demonstrated that anticholinergics are specific therapy for peptic ulcer and it has never been satisfactorily demonstrated that they enhance the healing of such a lesion. Their role is purely that of adjunct therapy, their major purpose being relief of pain due to decreased gastric motility. Their antisecretory effect is of assistance in obtaining the proper neutralization for ulcer healing. The primary purpose of this study was to examine the safety of this drug in elderly patients.

Eighteen patients had an excellent symptomatic response, 11 a good response, and 3 an inadequate response. All 3 patients with an inadequate response eventually submitted to surgery. Of these, 2 with stomal ulcers had a transthoracic vagotomy, and 1 with a gastric lesion (proved surgically to be benign) underwent gastric resection.

Xerostomia. Six patients complained of xerostomia, but it was not distressing enough to require discontinuance of therapy. Although most were receiving Piptal in a dosage of 10 mg. four times daily, xerostomia also occurred during 5-mg. dosage.

Constipation. No major change in bowel habits was noted. All patients who reported any degree of constipation prior to the institution of Piptal therapy were given small amounts of magnesium oxide in combination with other alkalies. Therefore, an estimation of the effect of Piptal on constipation cannot be made, except to state that no significant constipating effect was observed.

DISCUSSION

The physician today is being consulted with increasing frequency by patients in the older age groups concerning symptoms referable to active peptic ulcer. Therapy for these patients is obviously made more difficult by the changes, both physiologic and psychologic, which take place in association with the aging process.

Unfortunately the advent of newer synthetic anticholinergics has not been of much assistance in the treatment of these patients, because of distressing side-effects. It is not generally recognized that the most disturbing complication in the anticholinergic treatment of peptic ulcer is the precipitation of active glaucoma in patients in whom this disease is incipient. Since the destructive effects of glaucoma on the retina are usually slow in progression and without overt manifestations, the ophthalmologist is frequently the first person to discover them. At this stage the effects may have become irreparable, with permanent visual damage and ultimate blindness. It is essential that the physician who is daily in contact with geriatric patients (many of whom have diges-

tive complaints) be made aware of the inherent danger to the retina by the careless use of unselected parasympatholytic drugs. Instruction in the use of the Berens-Tolman ocular hypertension indicator should be included in the training of every physician who may utilize atropine or atropine-like drugs. Not only will routine measurement of intraocular tension prevent precipitation of glaucoma by the uncontrolled use of parasympatholytic drugs, but many cases of early glaucoma will be revealed and referred for adequate ophthalmologic care. Such a prophylactic program should receive wide attention.

The anticholinergic drug (Piptal) under study did not exert any significant influence on intraocular tension in our series of 32 patients, even in the 2 in whom pre-existing compensated glaucoma was demonstrable.

The other most distressing complication of anticholinergic therapy is urinary retention. Piptal failed to have any effect upon the detrusor muscle of the bladder, even in those patients with distinct evidence of bladder-neck obstruction.

It appears, therefore, that Piptal is a safe drug for routine use in geriatric patients with peptic ulcer. There would seem to be little fear of inducing ocular complications or urinary retention. Piptal is best used adjunctively in association with adequate alkali therapy, sedation when necessary, and proper dietary management.

SUMMARY AND CONCLUSIONS

Associated with the use of most synthetic parasympatholytic drugs and belladonna in the treatment of peptic ulcer in the aged, the most distressing and potentially dangerous side-effects are increased intraocular tension and acute urinary retention.

Urinary flow and intraocular tension have been measured in a series of 32 men with peptic ulcer. It has been demonstrated that Piptal (a recently introduced anticholinergic agent), in dosages that are therapeutically effective for peptic ulcer, does not induce either urinary retention or glaucoma.

It is concluded that Piptal is a valuable cholinolytic adjunct in the management of peptic ulcer in the older age groups, because it provides relief of ulcer symptoms in most cases, but does not affect the bladder or the eye. It appears, therefore, to be a safe preparation for use in this increasing segment of the population, until now denied the use of other available anticholinergic drugs.

Acknowledgment

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REFERENCES

1. Mulsow, F. W.: Peptic ulcer of the aged, *Am. J. Digest. Dis.* **8:** 112 (Apr.) 1941.
2. White, F. W.: The incidence of gastroduodenal ulcer, *in* Peptic Ulcer, ed. by D. J. Sandweiss. Philadelphia, W. B. Saunders Co., 1951, p. 185.
3. Lemoine, A. N., Jr.: Glaucoma: statistical review of 816 patients with 1,112 glaucomatous eyes, *Am. J. Ophth.* **33:** 1353 (Sept.) 1950.

4. BERENS, C., AND NILSON, E. L.: Etiology of so-called chronic simple glaucoma: possible role of focal infection, especially in the nasal accessory sinuses, *Tr. Am. Acad. Ophth.* **48:** 121 (Jan.-Feb.) 1944.
5. ULLMAN, E. V., AND MOSSMAN, F. D.: Glaucoma and orally administered belladonna, *Northwest Med.* **48:** 245 (Apr.) 1949.
6. LARMANDE, A. M., AND TOULANT, M.: Le danger pour l'oeil des prescriptions médicales et chirurgicales d'atropine et de belladone, *Presse méd.* **59:** 1611 (Dec. 5) 1951.
7. SCHUELER, F. W.: Unpublished data.
8. CHEN, J. Y.: Anti-spasmodic activity and toxicity of N-ethyl-3-piperidyl benzilate methobromide, *Fed. Proc.* **13:** 343 (March) 1954.
9. MCHARDY, G., AND others: Secretory and motility inhibitors; an evaluation of four newer anticholinergic agents, *Am. J. Gastroenterol.* **24:** 601 (Dec.) 1955.
10. RIESE, J. A.: Peptic ulcer management with JB 323 (Piptal), a new anticholinergic, *Am. J. Gastroenterol.* **23:** 223 (March) 1955.
11. KAUFMAN, J.: Personal communication.

A TWO-YEAR COMPARATIVE STUDY OF ATARAXICS IN NEUROPSYCHIATRIC PATIENTS*

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During the past two years (1954 and 1955), clinical trials of ataraxic drugs have been conducted in 2,360 neuropsychiatric patients, including those with schizophrenia, manic-depressive psychosis, epilepsy, Huntington's chorea, meningo-encephalitis syphilitica, and senile and arteriosclerotic psychoses.

METHODS

Medication was given orally to all patients who would accept it. Those who would not cooperate received it parenterally. Certain patients were also used for the clinical trial of concentrated injectible solutions of reserpine and chlorpromazine. The patients were evaluated mentally and physically, and routine laboratory tests performed, before drug therapy was begun. In daily records were noted such factors as the kind of drug used, the dosage, time of administration, physical and mental reactions, and sleep habits. Biweekly interviews with patients and nurses were recorded.

On the first 200 patients receiving chlorpromazine, the following laboratory determinations were made: hemoglobin, leukocyte count, eosinophil count, cephalin flocculation, sedimentation rate, hematocrit, serum protein concentration, A/G ratio, and blood sugar level. As repeated tests showed no significant changes, and there were no side-effects of even a slightly serious nature, only routine laboratory tests were performed subsequently.

Each patient who was able to go home was given a prescription for the agent which produced improvement, and a card recommending that he continue to take the medication faithfully and work at a useful occupation. Being able to go home did not necessarily mean that complete remission had been obtained. Our therapeutic goal was a normal personality function. In many cases of complete remission the patients should be at home, but instead they remain in the hospital because there is no one to care for them.

RESULTS

Reserpine

Two years ago (1954), 350 patients were selected from among 451 whose disease was chronic. During the year 1953 these patients had received 11,320 shock treatments. They were maintained in a fairly quiet, improved condition. Twenty per cent were able to go home. All except a few returned to the hospital when the effect of shock therapy wore off.

After receiving reserpine for one to six months, 150 (42.8 per cent) of these

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patients were able to return to their homes. Of this group, 20 per cent came back to the hospital, most of them having discontinued the medication. Those who remained in the hospital improved in clarity of thought, coherence, orientation, rapport with associates, cleanliness, application to gainful occupation, interest in life, pride in self, responsiveness, and ability to live quietly and peacefully (1). The expression of delusional trends and hallucinatory experiences diminished.

Many patients remained at home after two years of therapy, still taking the dosage of reserpine prescribed when they left the hospital. It is astonishing and gratifying to consider the results in patients who had spent anywhere from ten to thirty years in the wards for the disturbed. They had been only slightly and temporarily benefited by shock and other therapies, but are now at home earning their own living.

A few patients improved within four days, but many required months of therapy with increasing dosages of reserpine before a response was noted. For example, a catatonic schizophrenic patient, hospitalized at the age of 17 years and secluded on the disturbed ward for five years, was assaultive, denudative, coprophagic, noisy and untidy. Shock therapy, on a schedule of two or three treatments daily diminished to one weekly, calmed her for only short periods and left her confused. She apparently regressed. After ten months of therapy with reserpine in increasing dosages up to 30 mg. daily, she began to improve. Three months later, she was no longer assaultive, but was oriented and coherent. She practiced typewriting, was neat and clean about her person, attended amusements, and helped with ward work. Occasionally, she had outbursts of temper when crossed. The dosage of reserpine was reduced to 10 mg. daily. She became well enough to go home but had to wait a few weeks until her mother, who was also a patient, improved sufficiently to leave the hospital. Because her mother was receiving chlorpromazine, it was considered advisable to change the girl's medication to this drug also. Twelve days before she left the hospital, the change was made to 150 mg. of chlorpromazine three times a day. She had one attack of syncope from hypotension after the first dose, but none later. She was sent home with a prescription for 100 mg. of chlorpromazine four times a day. She writes to me each week. Her typewriting has improved, and she is now typing her father's business letters.

Nine per cent of this group were tested psychologically. The results were well correlated with the psychiatric and social findings.

A second group of 530 patients also received reserpine. Included were many patients with hebephrenic schizophrenia and arteriosclerotic psychosis, as well as those receiving a second course of reserpine after unsatisfactory results from the first course. The remission rate in this group was 4.1 per cent (Table 1).

Side-effects of reserpine included ptyalism, tremor, and muscular aches and pains. Parkinsonism developed in 3 of 1,000 patients treated with this drug. One patient, who had been assaultive, noisy, and self-destructive in response to her paranoid delusional trends, had taken 4 mg. of Serpasil (reserpine, Ciba) twice a day for two years. In June 1955, she went home with a prescription for that amount. She was normal when she left the hospital and continued to be

TABLE 1

Results of Long-Term (Two Months to Two Years) Administration of a Series of Ataraxics*

	Placebo	Miltown	Frenquel	Thorazine	Raudixin	Reserpine
Daily dosage (mg.)		1,600–8,800	80–400	225–1,800	400–1,200	1–30
Number of patients	300	301	350	350	200	530
Complete remission	—	3.0*	2.0	3.5	—	4.1
Greatly improved	—	29.0	23.7	49.6	—	12.6
Considerably improved	—	50.0	47.4	11.5	13.9	44.8
Total improved	—	82.0	73.1	64.6	13.9	61.5
No change	100	17.5	26.9	34.3	86.1	36.5
Made worse	—	0.5	—	1.1	—	2.0

* All figures pertaining to the degree of improvement are percentages.

normal mentally. However, a fine tremor of her muscles developed, and she returned in February 1956 for adjustment of her medication. She was given meprobamate (Miltown) in a dosage of two 400-mg. tablets twice daily. The tremor disappeared and her mental status remains normal.

In comparative tests with preparations of *Rauwolfia canescens, vomitoria, heterophylla* and *serpentina*, no difference in effects could be observed. The 4-mg. tablets of Reserpoid (reserpine, Upjohn) and 5-mg. and 10-mg. tablets of Sandril (reserpine, Lilly) are convenient when large dosages are required. Concentrated Sandril solution given by dropper is the easiest form in which to administer reserpine to disturbed patients.

Chlorpromazine

Chlorpromazine (Thorazine—Smith, Kline & French) was given to 350 patients. Some received it for two years without side-effects. Dermatitis was the cause of temporary discontinuance in the greatest number of instances. In patients taking a second course of chlorpromazine more skin rashes developed than in those whose first course was uninterrupted. No parkinsonism, agranulocytosis, or jaundice occurred despite relatively high dosages.

The lowest maintenance dosage was 225 mg., and the highest 1,800 mg. daily. Chlorpromazine was given orally, unless even crushed tablets were refused; in this case, it was administered parenterally until the patient accepted it by mouth. Chlorpromazine from ampuls was mixed with fruit juice and given to a few patients.

In the group treated with chlorpromazine, complete remission occurred in 4.1 per cent. Combined with meprobamate, chlorpromazine proved highly satisfactory in refractory cases. No side-effects were observed. Hoch suggests that "the primitive fight-flight response has been dampened by chlorpromazine and that this underlies many of the beneficial changes" (2).

Meprobamate

Meprobamate (Miltown, Wallace) was administered to 300 patients. There was recovery in 3 per cent, great improvement in 29 per cent, and considerable

improvement in 50 per cent. Little change could be noted in 18 per cent (Table 1). Meprobamate dispelled delusions and hallucinations and reduced the tensions and anxiety that produced noisy, assaultive hyperkinetic behavior. It was an excellent somnifacient. Its safety was proved when a patient took sixty-six 400-mg. tablets (26.5 Gm.) and recovered in forty-eight hours with no sequelae. Except for drowsiness and hypotension following large doses, no side-effects occurred.

Berger states: "Miltown 400 mg./Kg. given to five monkeys produced flaccid paralysis lasting seven hours. Even after these large doses, respiration and heart beat were normal and all animals recovered spontaneously without any immediate or delayed ill effects. Repeated doses of the drug were also well tolerated. Emesis or anorexia was not observed during or following the administration of Miltown. Large quantities, when offered in food for periods as long as fifteen months, are tolerated without ill effect by young and old animals as well as by pregnant and nursing females" (3).

Meprobamate seemed to be the most popular ataraxic among the patients. Many requested it after it was discontinued because the supply was limited. Hyperhidrosis was relieved and the acrid odor of sudoral secretion, characteristic of certain patients, was mitigated. Because of its soporific action and lack of side-effects, it is one of the most useful ataraxics. It can be combined with reserpine or chlorpromazine to good advantage when insomnia occurs.

Psychologic findings in a sample of 100 of the patients receiving meprobamate confirmed the restorative qualities of this agent.

Azacyclonol

Azacyclonol (Frenquel, Merrell) was used in 350 patients. It was helpful in some cases of active hallucination, particularly in patients whose behavior was hyperkinetic and assaultive in response to their delusional trends. Its action, in disease states that appeared to be in the same category, was variable. A few outstanding results were obtained in chronic disease states. In acute hallucinatory episodes of recent development, results were less informative. Many hallucinatory episodes described as recent may have been preceded by similar ones in early childhood and adolescence. A careful history is necessary to bring this out. So-called recent cases may in reality be chronic, and thus the drug is often mistakenly recorded as being effective in recent cases. Rinaldi, Rudy and Himwich state that "Frenquel does not display any hypnotic action to account for its tranquilizing effect, nor does it cause a fall in blood pressure" (4).

Rauwolfia root

The whole root of *Rauwolfia serpentina* (Raudixin, Squibb) in a daily dosage of 400 to 1,200 mg. was of particular value in senile and arteriosclerotic psychoses. Its side-effects were similar to, but less marked than, those of reserpine.

Ethchlorvynol

This drug is being used, as Placidyl (Abbott), in a pilot study with 30 patients. It seems to show promise, not only as a hypnotic but as an anticonvulsant, in accordance with findings in experimental animals (5–8).

Pipradol

Pipradol (Meratran, Merrell) proved to be a useful analeptic when used in conjunction with reserpine and meprobamate. It cleared the thinking in confused senile and arteriosclerotic patients. Himwich and Rinaldi found that the pharmacologic action of pipradol is centered in the cortical and subcortical areas. Evidence of this action is found in such clinical effects as improved attention and interest and the alleviation of depression (9). The usefulness of pipradol in the emotional fatigue syndrome, and in increasing work activity has been confirmed by Antos (10). In our experience, it was most helpful in patients with decreased drive and conative function, and in the apathy and mutism of catatonic schizophrenia. In a few instances, it had to be discontinued when the patient became assaultively hyperactive.

Methyl-phenidylacetate

This drug (Ritalin, Ciba) is psychoanaleptic, and was most effective in apathetic, negativistic, dull, inert individuals. They became stimulated to cleanliness and activity. The dosage varied. Some patients improved with 10 mg. three times daily, whereas others required 20 mg. four times a day. One investigator has reported "little or no increase in motor activity above normal" (11). A few of the patients in this series became assaultive and overactive, even with small dosages, and the medication had to be discontinued.

Comparative study

During the course of the studies reported, it became apparent that some patients in a given diagnostic category improved markedly, whereas others in

TABLE 2

Results of Four-Week Trial of Each Ataraxic in Rotation, Interrupted by Placebo, in Comparable Groups of 28 Patients*

(Total number of patients receiving each drug = 196)

	Placebo	Miltown	Frenquel	Thorazine	Placebo	Raudixin	Reserpine
Dosage (twice daily)	Two 5-mg. tablets	Two 400-mg. tablets	Two 20-mg. tablets	Two 50-mg. tablets	Two 5-mg. tablets	Two 100-mg. tablets	Two 1-mg. tablets
Number of patients	196	196	196	196	196	196	196
Greatly improved	—	—	3.57*	6.89	6.06	3.45	5.41
Considerably improved	19.36	11.11	21.42	31.04	18.18	17.11	8.11
Some improvement	48.38	48.14	35.72	31.04	18.18	41.50	48.64
Total improved	67.74	59.25	60.71	68.97	42.42	62.06	62.16
No change	29.04	29.63	21.43	17.25	45.45	34.50	18.92
Made worse	3.22	11.12	17.86	13.78	12.13	3.44	18.92

* All figures pertaining to the degree of improvement are percentages.

the same group, having similar symptomatology and psychodynamic structure, did not improve. Perhaps the patients were wrongly classified, or possibly the chemical effect of the drug or its site of action in the brain differed from patient to patient.

In an effort to answer the question "Which ataraxic?" a double-blind study was carried out, using 5 drugs and 2 placebo preparations. It was hoped that

TABLE 3

Average Fall in Blood Pressure (mm. Hg) During a One-Month Trial of Ataraxic Drugs

	Placebo	Miltown	Frenquel	Thora-zine	Placebo	Raudixin	Reserpine
Systolic difference	3	5	4	6	3	8	8
Diastolic difference	−3	−1	−3	−2	−6	−5	−2

TABLE 4

Average Fall in Blood Pressure (mm. Hg) During a Long-Term Trial (2 mo. to 2 yr.) of Ataraxic Drugs

	Placebo	Miltown	Frenquel	Thorazine	Placebo	Raudixin	Reserpine
Systolic difference	—	15	12	27	—	36	37
Diastolic difference	—	11	7	10	—	18	16

TABLE 5

Side-Effects

	Miltown	Frenquel	Thorazine	Raudixin	Reserpine
Aching in arms and legs	−	−	+	+	+
Agranulocytosis	−	−	−	−	−
Constipation	−	−	+	−	−
Dermatitis	−	−	+	−	−
Depression	−	−	+	−	+
Diarrhea	−	−	−	−	+
Dizziness	−	−	+	−	+
Dryness of mouth	−	−	+	−	−
Enuresis	−	−	−	−	+
Jaundice	−	−	−	−	−
Lactation (with abcess)	−	−	+	−	−
Headache or sinusitis	−	−	−	−	+
Miosis	−	−	+	−	+
Nasal congestion	−	−	−	−	+
Nausea and vomiting	−	−	slight	−	+
Nightmares	−	−	few	−	few
Edema of face and extremities	−	−	slight	−	slight
Parkinsonism	−	−	−	−	+ [3]
Postural disturbance	−	−	−	−	+ [3]
Photosensitivity	−	−	+	−	−
Ptyalism	−	−	−	−	+
Tachycardia	−	−	+	−	−
Tremulousness	−	−	+	−	+

this study might furnish a clue as to the type of patient responding to each drug.

One hundred and ninety-six patients, who were classified as to such factors as diagnosis, mental and physical condition, and duration of psychosis, were divided into comparable groups of 28 patients each. They received each medication successively for one month. The drugs used were meprobamate, azacyclonol, chlorpromazine, Rauwolfia root, and reserpine. Obviously, the administration of a drug for one month does not allow sufficient time for the best results; neither does the use of an arbitrary dosage constitute optimal therapeutic management. Each ataraxic should be carefully titrated to the response of the individual.

Some ataraxics, especially the Rauwolfia preparations and chlorpromazine, have prolonged action. Therefore the pharmacist, who alone knew the codes, was requested to separate the courses of drug administration by a period of placebo administration, so that the effect of a specific drug would not be carried over and influence the effect of the succeeding drug. A similarly planned study, allowing three months for each course of drug administration would probably yield more accurate results.

It was most enlightening to observe patients improve or regress as they changed medications. Eventually, each patient received the drug that produced the most improvement in his case. Tables 2 through 5 show the results with each drug in terms of symptomatic improvement, effects on blood pressure and side-effects.

DISCUSSION

Ataraxic drugs have brought about a profound change in the appearance and activities of our hospital. During the past eighteen months, no treatment other than chemotherapy and supportive psychotherapy has been given. No shock therapy of any kind has been used. All patients, including those in the so-called disturbed and violent wards, are quiet and orderly. All patients wear clothing, and temporary seclusion is necessary only occasionally.

There still are some dull, inert patients who soil themselves and take no interest in life beyond eating. There also are some deluded, manneristic patients with hallucinations, but the accident rate is almost nil, the number of convulsive seizures has been cut in half, and the destruction of clothing and property has all but ceased.

During the year before ataraxics were given, while intensive shock therapy was being used, 20 per cent of patients were able to go home. Most of them returned within a few weeks or months. During the first year that ataraxics alone were given, 49 per cent of patients were able to go home and only 25 per cent returned. Many of the latter group had discontinued the medication, or could not afford to continue buying it. Many patients in the hospital are waiting to go home after eighteen months of restoration. For the first time in several years, the hospital has a sizable number of vacancies.

Relapse occurred from four days to eight months after the discontinuation of medication. All patients who discontinued medication have been rehospitalized.

Ataraxics have suspensive rather than curative action. Kinross-Wright has suggested the discontinuation of chlorpromazine "within a month following discharge from the hospital for those with acute illness, without paranoid features or evidence of lifelong personality disturbance, who are under self-limited or remedial stress" (12).

Patients returning from a leave of absence in a disturbed condition are less disturbed than they would be had they taken no tranquilizing drug during their former admission. Most of them are in better condition when brought back to the hospital than they previously were when going on leave following shock therapy.

The action of ataraxic agents is slightly more rapid when they are given parenterally than when they are given by mouth, but sufficiently large oral doses will quiet the most disturbed patient. The dosage must be individualized.

Shock therapies, with their inevitable use of force, engender an insane asylum atmosphere in a State Hospital. In contrast, the administration of ataraxics creates hospital-like, hopeful surroundings. The hospital attendants have, through extensive chart-making, note-taking, increased observation of each patient, and the giving of 10 new parenteral and oral medications, become more proficient and observant, and have acquired some nursing skills that they did not previously possess.

SUMMARY AND CONCLUSIONS

Clinical studies are presented of 2,360 neuropsychiatric hospital patients treated with reserpine, chlorpromazine, meprobamate, azacyclonol, Rauwolfia root and ethchlorvynol.

Some patients experience more improvement with one ataraxic than with another. The reason for this is not evident.

The impact of these drugs on the patients and on the hospital personnel has been remarkable. Even some patients who had been on the disturbed wards for many years could be discharged, and remain at home while receiving medication. The results have been such that chemotherapy is now believed to be the most efficacious and the safest treatment for neuropsychiatric patients.

The combination of ataraxics with the analeptics, pipradol and/or methylphenidylacetate, is advantageous in inert, dull, retarded, depressed, resistive patients.

A double-blind study of 5 ataraxic drugs was carried out in 196 patients. The longest duration of beneficial effect was obtained with reserpine. The highest rate of improvement was achieved with chlorpromazine—68.9 per cent versus 62.1 per cent with reserpine. The peak of improvement in 67.7 per cent of patients occurred in the four weeks following omission of reserpine therapy, while the patients were receiving a placebo. This is evidence of the prolonged beneficial effect of reserpine.

The side-effects observed during treatment with reserpine, whole Rauwolfia root, and chlorpromazine were more annoying than serious. Meprobamate and azacyclonol had no side-effects. All of these drugs induced varying degrees of reduction in blood pressure.

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REFERENCES

1. Pennington, V. M.: The use of reserpine (Serpasil) in three hundred and fifty neuropsychiatric cases. (Read at the Regional Research Conference, University of Texas, Galveston, February 18, 1953.) Washington, D. C., American Psychiatric Assoc., Research Report No. 1, 1955, p. 105.
2. Hoch, P. H.: The effect of chlorpromazine on moderate and mild mental and emotional disturbances, *in* Chlorpromazine and Mental Health Symposium. Philadelphia, Lea & Febiger, 1955.
3. Berger, F. M.: The pharmacological properties of 2-methyl-N-propyl-1,3-propanediol dicarbamate (Miltown), a new interneuronal blocking agent, *J. Pharmacol. & Exper. Therap.* **112:** 413, 1954.
4. Rinaldi, F., and Himwich, H. E.: The use of Frenquel in the treatment of disturbed patients with psychoses of long duration, *Am. J. Psychiat.* **112:** 343, 1955.
5. (a) Margolin, S.; Perlman, P.; Villani, F., and McGavack, T. H.: A new class of hypnotics: unsaturated carbinols, *Science* **114:** 384, 1951; (b) Papa, D.; Villani, F., and Ginsberg, H.: A new class of hypnotics: unsaturated carbinols, *Arch. Biochem.* **33:** 482, 1951.
6. P'an, S. Y.; Gardocki, J. F.; Harfenist, M., and Bavley, A.: Pharmacology of vinyl ethynyl carbinols—a new class of central nervous system depressants, *J. Pharmacol. & Exper. Therap.* **107:** 459, 1952.
7. Swinyard, E. A.; Schiffman, D. O.; Brown, W. C.; Grewal, M. S., and Goodman, L. S.: Anticonvulsant properties of unsaturated carbinols, *Arch. internat. pharmacodyn.* **94:** 81, 1953.
8. McLamore, W. M.; Harfenist, M.; Bavley, A., and P'an, S. Y.: Hypnotics and anticonvulsants. I. Tertiary acetylenic carbinols, *J. Org. Chem.* **19:** 570, 1954.
9. Rinaldi, F., and Himwich, H. E.: Drugs affecting psychotic behavior and the function of the mesodiencephalic activating system, *Dis. Nerv. System* **16:** 3, 1955.
10. Antos, R. J.: Meratran. Use of a new antidepressant in internal medicine, *Southwestern Med.* **36:** 166, 1955.
11. Ferguson, J. T.: Treatment of reserpine-induced depression with a new analeptic: phenidylate, *Ann. New York Acad. Sc.* **61:** 101 (Apr. 15) 1955.
12. Kinross-Wright, V.: Formal Discussion of Denber, H.: Medical and other measures to be taken to keep the discharged patient from returning to the institution, *in* Chlorpromazine and Mental Health Symposium. Philadelphia, Lea & Febiger, 1955.

PRACTICAL CONSIDERATIONS IN FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT

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Functional disorders of the gastrointestinal tract are, in the main, disorders of the nervous system. They arise as disturbances in the nervous system and are transmitted to the gastrointestinal tract, where they become manifest. The gastrointestinal tract is particularly liable to these functional disorders (1).

It is impossible to draw hard and fast distinctions between disorders which are termed functional and those which are organic. A condition which originally would be classified as purely functional often causes serious and sometimes permanent morphologic changes, thus ending up as an organic condition (2). For example, functional cardiospasm, if left to itself, causes two serious organic changes—irreversible dilatation of the esophagus, and inflammation of the esophageal lining.

It is impossible to draw a sharp distinction between functional and organic gastrointestinal disorders, because of their possible association with a remote lesion in the body. We speak of the functional vomiting of pregnancy, although pregnancy is an organic condition. On the other hand, the anorexia and vomiting often associated with pulmonary tuberculosis (3) are not usually classified as functional, because an organic lesion of etiologic significance is present, even though it is not in the gut. This digestive disturbance, however, although it has an organic basis, seems to share an important characteristic of the clearly functional disorders, *i.e.*, it is effected through the nervous system. The pulmonary lesion apparently exerts an influence on the autonomic nervous system, which in turn acts on the stomach and causes the symptoms. There need not be an organic lesion in the nervous system, although organic neurologic lesions often cause severe alterations in the functions of the gut and may result in actual morphologic changes. Such organic neurologic diseases may originate either in the central nervous system or in the autonomic nerves which flow out from the central nervous system to form the peripheral innervation of the gastrointestinal tract. Whether the lesion be in the central or in the autonomic system, it acts through the autonomic nerves directly on the viscera. Thus a lesion in the central nervous system first affects the autonomic system and through the latter, the gastrointestinal tract.

Functional nervous disorders, however, are much more important in the causation of gastrointestinal disturbances than are the organic nervous diseases. Functional disorders are mainly a result of disturbances of the emotional life,

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and therefore they are called psychosomatic diseases. They can be considered a manifestation of a general psychoneurotic disturbance. Like organic neurologic diseases, they affect the enteron through the nerves which innervate it.

NERVE SUPPLY

It is obvious that in order to understand functional gastrointestinal disorders, some discussion of the physiology of visceral innervation is necessary. In this connection three systems of visceral nerve supply are important: 1) sympathetic, 2) parasympathetic, and 3) the intrinsic nerve supply (called the enteric nervous system).

The general action of the *sympathetic* fibers is to inhibit the motility of hollow viscera and to contract sphincters—the musculature of the body of the organ is relaxed and peristalsis is diminished, but the musculature of the sphincters becomes contracted, and the sphincters are closed. Thus sympathetic activity slows the passage of food through the alimentary canal. Correlated with this slowing of the passage of food is diminution of the secretion of juices and enzymes by the digestive glands. This reduction in the secretion of acid gastric juice (hypochlorhydria) is a characteristic of excessive sympathetic activity, as is also a diminution of pancreatic and intestinal ferments.

The *parasympathetic* fibers, on the other hand, have an activity which is opposite to that of the sympathetic fibers. In general, the parasympathetic fibers are excitants of the smooth muscle of the viscera. They encourage peristalsis and motility, and cause the sphincters to open by inhibiting contraction. Parasympathetic stimulation encourages the secretion of gastric juice and other digestive liquids.

The viscera also have an *intrinsic nerve supply* which is called the enteric nervous system. This system can function adequately without any synaptic connections with the central and autonomic nervous systems. If all the extrinsic nerve supply to the gastrointestinal tract should be severed, gastrointestinal activity will go on in an orderly fashion because of regulation by the enteric nervous system. There are two striking clinical applications of this fact. The first is that ganglionectomy and neurectomy can be carried out without fear of permanent disability of digestive function. The second is that lesions which cause destruction of central nervous connections are not important causes of gastrointestinal disturbances; but nervous conditions which cause irritability or instability of one of the other nervous systems can give rise to severe functional gastrointestinal disorders.

PARASYMPATHECOTONIA OR VAGOTONIA

Excessive irritability of the parasympathetic system is known as parasympathecotonia or vagotonia. The use of the term vagotonia to describe this condition is justified by the fact that the vagus contains the great parasympathetic innervation to almost the entire gastrointestinal tract. The exception is the lower portion of the large intestine and the rectum which are innervated by the pelvic nerve carrying the sacral parasympathetic outflow to this region. Para-

sympathecotonia is the more accurate term and is preferred in modern usage. It may affect any organ, but we shall confine ourselves to the gut.

In gastrointestinal parasympathecotonia the symptoms are the result of the disordered physiology which comprises hyperchlorhydria, hypermotility and relaxed sphincters. These symptoms include pyrosis or heartburn, rapid onset of a feeling of fullness after eating only a small amount, and either diarrhea or spastic constipation. Pain and tenderness in the abdominal wall may be present in some cases, but this is not necessarily an indication of organic disease. Even x-ray evidence, if not clear-cut, may be misleading; and if taken alone, cannot always be relied upon to indicate organic disease. A detailed history and physical examination are important for diagnosis and must not be substituted by the adjuncts of study.

The diagnosis of parasympathecotonia can be established, after ruling out organic disease, by the physical findings and by some simple tests. There may be evidence of the effect of vague activity on other organs. In an otherwise nervous person, a slow pulse, which indicates a vagotonic heart, is an important sign. Bronchial spasm, asthma, and arrhythmic breathing are other signs of vagus irritability. However, there may be no symptoms referable to other organs and, furthermore, not even the entire gastrointestinal tract may be parasympathecotonic. The stomach alone, or the large intestine, may be the only organ involved. Sometimes one organ (*e.g.*, the large intestine) is parasympathecotonic in some places and is just the opposite *i.e.*, sympathecotonic, in other places.

Tests which can be used to establish the diagnosis depend on the sensitivity of the paraympathetic to certain kinds of stimulation. The chemical stimulants most frequently employed are pilocarpine and acetylcholine. A dose of $\frac{1}{6}$ grain (0.01 Gm.) of pilocarpine hydrochloride when injected subcutaneously causes the following effects: salivation, lacrimation, vomiting, diarrhea, asthmatic breathing and perspiration. The intensity of the response is a measure of the irritability of the parasympathetic system. Acetylcholine in minute amounts also produces very strong parasympathetic effects, which can be relieved by atropine.

Another test depends on the oculocardiac reflex. The eyeball is compressed for about thirty seconds, but without causing pain. In a parasympathecotonic patient there is a slowing of the heartbeat and an induction of gastrointestinal effects, mainly referable to increased peristalsis. This test causes little reaction in a normal person and none in a sympathecotonic person.

In the differential diagnosis one must consider the organic gastrointestinal diseases, especially neoplasms and peptic ulcer. Peptic ulcer is frequently a sequel of gastric parasympathecotonia. In the differential diagnosis of parasympathecotonia, one must also consider cardiospasm and the various organic gastrointestinal disorders.

The prognosis is good once treatment is established. If psychologic factors such as worry, unhappiness and financial strain continue and the condition is not treated, more serious gastrointestinal conditions may ensue. Disappearance of the emotional disturbance alone may result in a "cure," but most cases are

chronic. Of course a patient's constitutional tendency toward an irritable parasympathetic nervous system cannot be cured, but his symptoms can be controlled and complications avoided. The treatment involves a bland diet, the use of antispasmodics such as atropine or belladonna and, in some cases, psychotherapy. The diet should contain plenty of bulk to help overcome the atonic constipation. Vitamin, mineral and protein intake must be adequate.

SYMPATHECOTONIA

When a patient has a constitutional tendency toward an irritable sympathetic nervous system, psychologic upsets may induce gastrointestinal sympathecotonia. However, it may develop without any particular psychologic circumstances, if the constitutional tendency is strong enough.

The symptoms develop from the disordered physiology, namely, relaxed musculature, closed sphincters and hypochlorhydria. The outstanding symptoms are an uncomfortable sensation in the epigastrium, distention, eructation of gas, and constipation. So-called anorexia nervosa is usually a sign of sympathecotonia. Physical examination usually reveals an asthenic individual with a soft abdomen.

The diagnosis of sympathecotonia is made only after ruling out organic disease. There are tests which detect hyperirritability of the sympathetic nerves. One of these is the adrenalin test, in which 1.0 cc of 1:1000 adrenalin solution is injected subcutaneously. In a sympathecotonic individual the pulse rate will increase by more than 30 per cent and/or there will be an increase in the systolic blood pressure of from 30 to 40 millimeters. Usually there is also an increase in the quantity of urine voided in the next twenty-four hours.

SYMPTOMS OF FUNCTIONAL DISORDERS

Pyrosis

Although pyrosis (heart-burn) frequently occurs in vagotonic patients, who have gastric hypersecretion, it does not necessarily follow that it is a result of this condition. Heart-burn is often a symptom among patients with normal or subnormal gastric secretion and achylia gastrica.

Specialized nerve fibers carry stimuli resulting in the various taste sensations. Some nerve fibers, when stimulated, produce sensations involving different varieties of touch, such as heat, cold, cramping or piercing. Therefore, it seems probable that there are "sensory acid" nerve fibers which, when stimulated, produce the sensation of heart-burn regardless of the nature of the stimulant, be it acid, neutral or alkaline.

Heart-burn as a symptom is significant only when it becomes persistent. It then indicates the presence of an abnormal stimulant due to organic disease.

Cardiospasm

Functional spasms of the sphincters form a group of disorders of which cardiospasm is the most important. Cardiospasm is a well defined disturbance of the swallowing function (4). It was formerly believed to be a spasm of the cardia,

but the gastroscope has disproved this idea. The disturbance consists rather of a failure of the diaphragmatic pinchcock in the lower esophagus (also called the hiatal pinchcock) to open at the approach of the bolus. A normal person can stand on his head with a full stomach and nothing will leak out, because the hiatal pinchcock is tightly closed. However, when the normal person swallows some food, a reflex opening of the pinchcock occurs and the food enters the cardia. In functional cardiospasm this reflex opening of the hiatal pinchcock is not coordinated with the approach of the bolus and the food remains in the esophagus. For this reason, some modern authors have discarded the term cardiospasm in favor of the phrase, "incoordination of the diaphragmatic pinchcock."

In advanced cases of cardiospasm with marked esophageal dilatation and elongation, on starting treatment with the mercury-filled dilators, it may be noted that the dilator passes with ease through the cardioesophageal orifice if properly guided under the fluoroscope. Further, the dilator may be moved up and down without the sensation of tugging which would suggest spasm at the cardioesophageal juncture. In these instances it is possible that 1) not only is the pinchcock not functioning properly, but the esophageal musculature is atonic, 2) there is deduplication of the mucosa just above the cardiac orifice with redundancy over the orifice, and 3) the sheer weight of food retained in the esophagus in these conditions results in the picture seen on x-ray examination.

Cardiospasm is an hysterical symptom and often appears when a patient finds himself in an emotional impasse in regard to his external situation.

The most prominent symptoms of cardiospasm are: dysphagia regarding both liquid and solid food, with relief upon ingestion of a warm liquid; gaseous eructation; and gurgling and retrosternal discomfort.

Diagnosis does not depend on symptoms, since they are similar to those in other conditions. The diagnosis is facilitated by fluoroscopy. In the normal subject barium passes quickly down the esophagus and then hesitates slightly before entering the cardia. In a case of cardiospasm the column of barium is seen to remain in the esophagus; its base is at the level of the diaphragm and it fills the proximal portion of the esophagus, which is often dilated and presents a smooth conical appearance. The esophagoscope can also help in making the diagnosis, if the trouble has been of fairly long duration. Upon esophagoscopy, the normal pink mucosa is seen to be replaced by a white, coated surface which is often wrinkled rather than smooth. The esophagus is also increased in length and is dilated above the hiatus. The lengthened esophagus is prevented by the diaphragm from passing downward, and hence presents a kinked appearance. The esophagus is very intolerant of the continued presence of anything, even its own secretions. Thus an inflammatory condition readily occurs, and dilation with other changes follow.

Cardiospasm may be a reflex reaction resulting from the transmission of stimuli through vagal nerve fibers in cases of chronic cholecystitis, pathologic conditions of the gastroduodenum, and chronic appendicitis.

The differential diagnosis must take into account angina pectoris (which also causes substernal discomfort) and some organic lesions, especially neoplasms of

the esophagus and cardiac end of the stomach. Also to be considered are the less definite functional conditions, especially the so-called nervous vomiting.

The prognosis is good, as the spasm can be relieved. If irreversible changes in the esophagus have taken place, however, there will remain a dilated and elongated esophagus. It may be necessary to destroy the function of the hiatal pinchcock in order to afford relief.

The treatment of cardiospasm should be at first medical and psychologic. Antispasmodic drugs are beneficial. If the emotional disturbance causing the condition is cleared up, the cardiospasm may be relieved. If conservative treatment fails, dilatation of the cardiac orifice should be attempted.

Dilation of the lower esophagus effects relief by destroying or impairing the function of the pinchcock. Coordination is not restored. The fibers are stretched until the pinchcock cannot close; thus it remains open permanently so that food may enter the stomach without the necessity of a reflex opening of the pinchcock. The successful treatment of cardiospasm by cervicodorsal sympathectomy has been reported, but this procedure hardly seems worthwhile in view of the other methods at our disposal. Occasionally, when lengthening is marked, esophagogastrostomy must be performed.

Sphincter spasm

Spasms of the pylorus, of the ileocolic sphincter, and of the internal sphincter of the anus also may be symptoms of a functional disorder. They are most apt to be found in patients with a constitutional sympathecotonia, since this condition involves spasm of the sphincter.

Pylorospasm is sometimes observed in infants. In such cases a congenital sympathetic irritability is probably present. As a result of persistent spasms, the pyloric sphincter muscle probably undergoes hypertrophic changes, with the ultimate development of stenosis. In pylorospasm, pain in the epigastrium and at the left second costochondral junction, with vomiting some hours after eating, are the usual complaints. Ileocolic spasm may manifest itself by pain in the right lower quadrant and gas formation. The outstanding symptom of spasm of the internal sphincter of the anus is constipation.

The diagnosis of pylorospasm and spasm of the ileocecal valve should be made by x-ray studies, at which time organic disease can be ruled out. Spasm of the internal sphincter of the anus can be diagnosed by digital examination or with the proctoscope. In pylorospasm, gastric analysis will show a fasting gastric content of more than 100 cc., with mucus. However, this is by no means pathognomic, since an organic lesion may be the underlying cause of the retention.

In the differential diagnosis of functional spasms, care must be taken to rule out organic diseases which, in the gastrointestinal tract, are more common than functional ones. In the case of pylorospasm, carcinoma of the stomach and peptic ulcer should be considered. In the case of spasm of the ileocecal valve, one should consider carcinoma, chronic granulomas of the cecum and lower ileum, regional ileitis and chronic appendicitis.

The treatment of functional spasm is dietary and sedative. If the patient is

in a state of great emotional distress, psychotherapy may be indicated. Barbiturates and codeine may be helpful. Idiosyncrasies to certain foods may bring on the spasms by stimulating the reflexes; these foods should be eliminated from the diet.

Constipation

In some functional gastrointestinal disorders, constipation is the only symptom. Faulty elimination may be caused by numerous organic conditions which obstruct the lumen of the bowel by growing into it or by pressing on it from outside. In such cases, the condition is called *obstipation*; the term constipation is reserved for the functional disorder.

Constipation may be incompleteness or delay in evacuation, a tendency to abnormal hardness and dryness, or a reduction in the quantity of the feces. As a general rule, constipation exists when bowel movements occur less frequently than once in three days. However, constipation may exist with even a daily evacuation, when the progress of the feces through the colon is too slow. Usually, chronic constipation is a psychogenic disorder, and the psychologic findings are typical, based on a pessimistic, defeated attitude.

Constipation may be divided into two general types, the atonic form and the spastic. The atonic form is often associated with an asthenic habitus, whereas the spastic form often occurs in the hypersthenic or robust individual. However, part of the colon may be hypertonic, and another part may be atonic in the same individual.

Atonic constipation is characterized by: 1) atony of the muscles, 2) loss of irritability of the rectum, and 3) lack of propulsive force. Atonic constipation would seem to be sympathecotonic, and spastic constipation, parasympathecotonic.

Among the immediate causes of constipation are: lack of sleep, voluntary suppression of the call of nature, lack of physical exercise, emotional strain, irregular meals, psychic depression and hasty defecation. The role of mental strain and emotional factors, especially hypochondria, is important.

The most common form of constipation, known as *dyschesia* or *proctogenic constipation*, is a derangement of the functions of the lower end of the bowel. The next two most common sites of the disorder are the cecum and sigmoid flexure. In some cases the muscular coat of the lower end of the colon becomes more and more relaxed, distended and weakened, owing to excessive accumulation of feces; finally it loses the power to contract against the dry mass awaiting expulsion.

In infants there is sometimes observed an enormous dilatation of the colon with chronic constipation. This condition is known as Hirschsprung's disease, which is believed to be a congenital sympathecotonic condition.

The *symptoms* of constipation vary widely. Some patients are symptomless. In others, symptoms range from local to general, as follows: 1) colonic, characterized by distention, a feeling of weight and fullness, flatulence, colicky pains and borborygmi (the noises made by flatus in the bowels), and 2) systemic, including headaches, lassitude, anorexia, nausea, insomnia, and halitosis.

There is little doubt that many symptoms of constipation are produced reflexly by irritation of the mucous membrane and distention of the muscular coat of the colon. Furthermore, many symptoms and conditions may be produced by the pressure of fecal accumulation in the colon. Pressure on the veins causes hemorrhoids and pelvic pain. Pruritus ani may result from pressure on the nerves of the rectum. Pressure on the sacral nerves may induce pain, referred principally to the sacrococcygeal region.

Attacks of diarrhea may occur in persons suffering from constipation. Such attacks may be due to irritation caused by impaction or excessive retention of the intestinal contents, or from purgatives used to excess. In cases of fecal impaction in the rectum, the real condition may be obscured by a continuous diarrhea caused by irritation. In such cases the abdominal findings are not characteristic.

Physical examination will yield widely differing results depending on the type of constipation. In the atonic type, there are lax muscles and moderate distention with gas; the colon cannot be palpated. In the spastic type, on the other hand, the descending and sigmoid portions of the colon can often be palpated as firm cords, sensitive to pressure.

The stools vary in character and size within wide limits, ranging from small-caliber pencil stools in spastic constipation to large round masses in atonic constipation. Fecoliths or coproliths sometimes occur, most frequently in the cecum, rectum and sigmoid flexure. Fecoliths cause dilatation of the colon, and diverticuli may develop.

Direct diagnosis is easy and is suggested at once by the symptoms and especially by the history. X-ray examination following a barium meal will show the extent and type of constipation. In spastic constipation, there are contracted areas, and the haustra are of small diameter. In the atonic form, on the other hand, the x-ray picture shows relaxation and distention of the colon, with large haustra. In the spastic form the rectum fits closely around the examining finger. In the atonic form this is not the case; large fecal masses may be present and can be moulded with the finger.

It is important, in the differential diagnosis, to rule out organic obstipation due to mechanical obstruction. Rectal and sigmoidoscopic examinations are of the utmost importance whenever there is the slightest suspicion of a malignant condition. The need for ruling out organic involvement makes the use of x-ray studies practically mandatory.

The *prognosis* in constipation is favorable. Not only is it not fatal, but it can usually be cured. The longer the duration, the more difficult the treatment, but favorable results can be attained by the use of suitable diets, laxatives and tonics. Emotional disturbances and nervous conditions may have to be investigated and specially treated in some cases.

In the *treatment* of constipation the therapeutic problem is to restore a normal habit by re-educating the intestinal tract. As a general rule, the atonic forms require exercise, massage and other mechanical measures, roughage in the diet, and tonic hydrotherapy. The spastic forms, on the other hand, require relaxing

measures such as a bland diet, soothing hydrotherapy, and the use of antispasmodic drugs.

Purgatives and enemas afford temporary relief, but they may have harmful results if used often and should be avoided. Enemas are less harmful than purgatives.

The formation of good habits is highly important, and the patient should be instructed not to ignore the call of nature. Sometimes a change of diet is enough to effect a cure. However, there is no single diet for constipation. The needs of the individual must be taken into account, depending upon the type of constipation.

In severe atonic constipation, section of the sympathetic nerves may be beneficial.

Psychotherapy can be a useful adjunct; for instance, the patient who is upset by the fear of cancer should be reassured. In the spastic type, belladonna, atropine and valerian are helpful; one of these drugs should be given whenever a laxative is used, to obviate griping. A saturated solution of magnesium sulfate in the form of an enema will relax a spastic lower bowel.

Simple dyschesia may be treated with suppositories of cocoa butter. Obstinate cases may be treated by instructing the patient in measures to re-establish the tonicity of the rectal musculature, as follows: A retention enema of 3 ounces of a slightly warmed vegetable oil to be taken nightly before retiring. (One hour before the initial retention enema, a one-quart cleansing enema of soap suds should be used.) Expulsion of the oil may be avoided by assuming the knee-chest position while the oil is injected over a period of three minutes; this position should be maintained for another five minutes. The oil will break up partly into fatty acids which stimulate the rectal muscles to contraction; the remainder will act as a lubricant. With improvement of the dyschesia, the interval between injections of oil into the rectum is increased.

SUMMARY

A discussion of practical considerations in gastrointestinal functional disorders has been presented, including etiologic mechanisms and differential diagnosis.

The treatment of the various types of gastrointestinal functional disorders has been outlined, with particular stress on the treatment of constipation.

REFERENCES

1. Rossien, A. X.; Rappaport, E. M., and Rosenblum, L. A.: Clinical aspects of gastrointestinal functional disorders, *Bull. New York Med. Coll.* **12:** 47–69, 1949.
2. Rossien, A. X.: A practical interpretation of gastrointestinal symptoms, based on a three-year clinical study (introducing a new concise history sheet), *Rev. Gastroenterol.* **10:** 112–118 (Mar.–Apr.) 1943.
3. Rossien, A. X.: Association of tuberculosis with gastroenteritis. The problems of the gastroenterologist in tuberculosis, *Rev. Gastroenterol.* **19:** 29–38 (Jan.) 1952.
4. Weiss, E.: Cardiospasm. A psychosomatic disorder, *Psychosom. Med.* **6:** 58–70 (Jan.) 1944.

LARGE, INDURATED, BENIGN GASTRIC ULCERS IN PATIENTS OVER THE AGE OF 60

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With the increase in life expectancy and the decrease in surgical mortality, the proper management of gastric ulcer in the older patient takes on additional importance. In this connection, it is of value to call attention to the relatively frequent occurrence of large, indurated benign gastric ulcers (with a short or atypical clinical history) in persons over the age of 60.

These ulcers are often thought to be malignant because of the advanced age of the patient, the brief and suggestive clinical history, and the size and nature of the lesions upon x-ray examination. Four illustrative cases observed at Beth-El Hospital within the past two years are presented.

CASE REPORTS

Case 1

J. D., a 66-year-old white man, was admitted complaining of severe intermittent epigastric pain occurring at hourly intervals during the preceding four-day period. Although he had had some intermittent pain for the previous three weeks, which yielded to antispasmodics and antacids, he attributed the recent marked exacerbation to a dietary indiscretion and an emotional upset.

He had been treated for duodenal ulcer two years previously, and an x-ray study of the upper gastro-intestinal tract six months later showed only the sequelae of a duodenal ulcer. Until the onset of the present symptoms, there had been no difficulties.

During hospitalization the pain became more severe, requiring opiates for relief. X-ray examination showed a large ulcer crater on the lesser curvature high in the pars media, with induration of the adjacent walls (Fig. 1). Upon gastric analysis, free acid was present and the total acidity was within normal limits. Occult blood was found in the stool.

A subtotal gastrectomy was performed and a penetrating gastric ulcer 30 mm. in diameter was found high on the lesser curvature (Fig. 2). Its base and the surrounding portion of stomach were indurated. The crater edges were well defined. Microscopic examination of many sections revealed the characteristics of chronic gastric ulcer. There was no evidence of malignancy.

Case 2

I. E. was a 64-year-old white woman whose chief complaint was intermittent epigastric pain of one month's duration. There was irradiation of the pain across the flanks and into the back between the shoulders. Frequently severe at night, the pain was not related to meals. It was usually associated with belching and eructation and was relieved by milk and sodium carbonate. There was some tenderness in the epigastrium.

A cholecystectomy had been performed two years earlier, at which time the surgeon had noted a normal stomach. An x-ray study of the upper gastro-intestinal tract at that time had showed a hiatus hernia but no ulcer crater.

X-ray examination of the upper gastro-intestinal tract during the present admission

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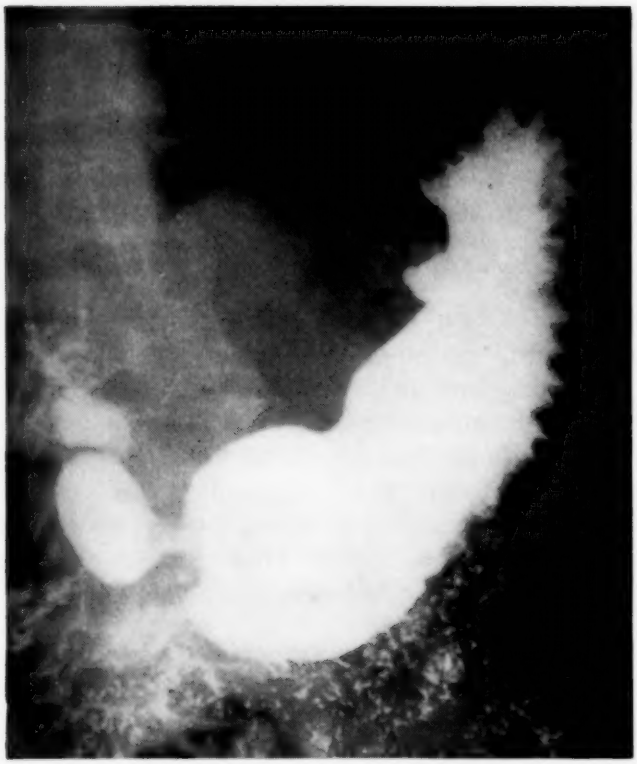

FIG. 1. *Case 1, J.D.* Barium contrast study of stomach showing indurated ulcer on lesser curvature.

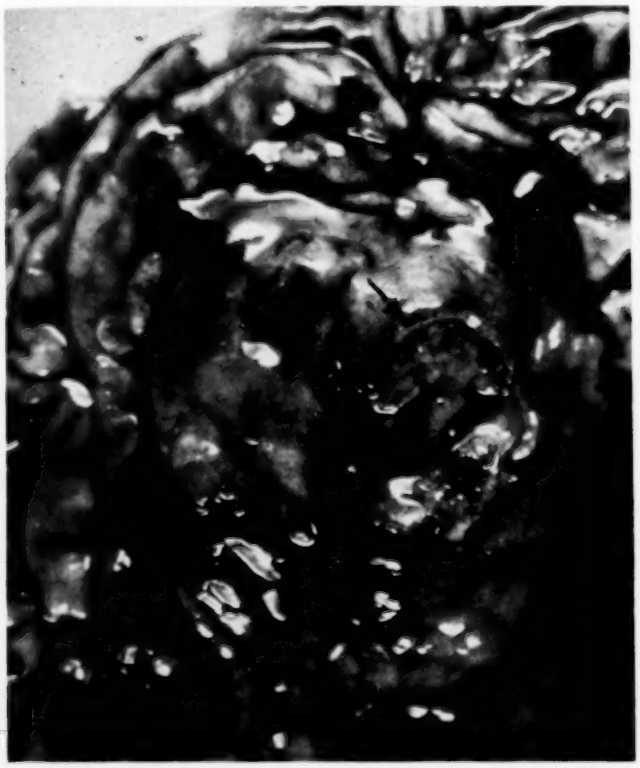

FIG. 2. *Case 1, J.D.* Surgically resected portion of stomach showing large penetrating ulcer.

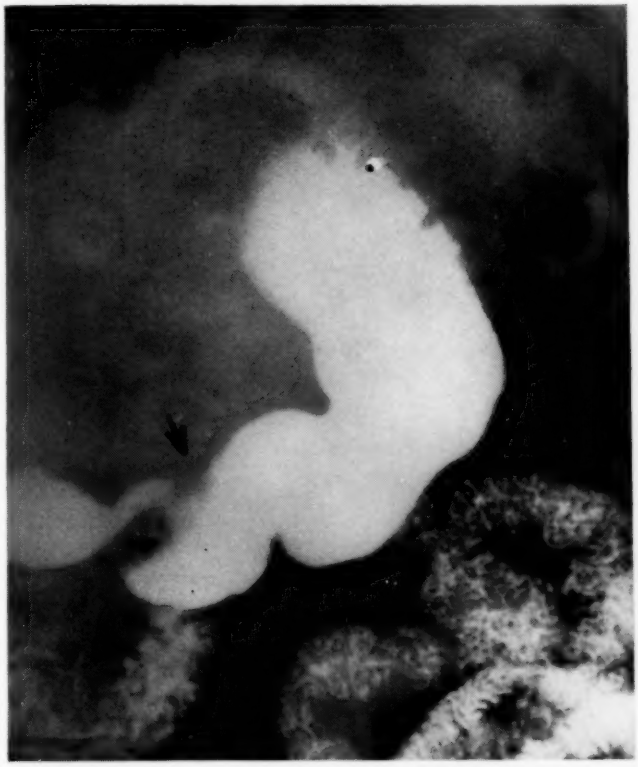

FIG. 3. *Case 2, I.E.* Barium contrast study of stomach showing ulcer crater with adjacent induration.

revealed a large ulcer crater with induration of the adjacent walls and a small diaphragmatic herniation of the stomach (Fig. 3). Gastric analysis showed marked hyperacidity. There was no occult blood in the stools.

A subtotal gastrectomy was performed and a gastric ulcer 15 mm. in diameter was found in the prepyloric region on the lesser curvature. The rugal folds were interrupted abruptly at the ulcer edge (Fig. 4).

Multiple sections showed the microscopic characteristics of chronic gastric ulcer with no evidence of malignancy.

Case 3

M. M. a 84-year-old white man, was admitted with evidence of massive gastro-intestinal hemorrhage consisting of coffee ground vomitus, tarry stools and marked anemia. Previous to the day of admission the only symptoms referable to the gastro-intestinal tract had been vague, mild heartburn and anorexia of two months' duration.

X-ray examination of the upper gastro-intestinal tract revealed a large ulcer crater on the lesser curvature in the pars media of the stomach, with indurated adjacent walls; there was no peristalsis (Fig. 5).

Subtotal gastrectomy was performed and a penetrating gastric ulcer 16 mm. in diameter was found on the lesser curvature. A broad ring of induration surrounded the well-defined ulcer edge (Fig. 6). Examination of many microscopic sections revealed the characteristics of chronic gastric ulcer. There was some glandular atypia at the ulcer edge, but no evidence of infiltration. Although the operative procedure was well tolerated and the immediate postoperative course uneventful, the patient died suddenly on the third postoperative day.

FIG. 4. *Case 2, I.E.* Surgically resected portion of stomach showing large prepyloric ulcer.

Postmortem examination revealed advanced calcific atheromatous degeneration of the markedly narrowed coronary arteries, and pulmonary edema.

Case 4

L. I., a 65-year-old white man, was admitted on August 22, 1955, complaining of abdominal pain radiating into both hypochondria, belching, severe thirst, and a 14-pound weight loss in the past twelve months.

"Ulcer" had been diagnosed clinically twenty-five years previously, and radiologically six years later. He had followed an ulcer regimen irregularly, and was asymptomatic until 1952. Since then he had had frequent severe attacks of epigastric pain beginning one and a half hours postprandially. During the two weeks prior to admission, he had become anoretic and the pain had become continuous and severe.

X-ray examination revealed a persistently deformed duodenal bulb and a peculiar slight irregularity along the lesser curvature. There was gastric hyperacidity, and occult blood was found in the stool. Symptoms subsided upon treatment with diet, antispasmodics and antacids. X-ray examination was repeated just before discharge, and a flat gastric ulcer surrounded by highly irregular mucosal folds was seen at the re-entrant angle.

The patient was readmitted three months later with recurrence of all symptoms in addition to nausea and vomiting. Another examination of the upper gastro-intestinal tract revealed a large ulcer crater within an intraluminal mass in the region of the lesser curvature of the pars media with adjacent indurated walls (Fig. 7).

Subtotal gastrectomy was performed, and a gastric ulcer 25 mm. in diameter was found on the lesser curvature, 6.0 cm. from the pylorus. The stomach wall surrounding the lesion was markedly thickened and the rugal folds were widened and hyperemic (Fig. 8). Micro-

FIG. 5. *Case 3, M.M.* Barium contrast study of stomach showing large ulcer crater with adjacent induration.

FIG. 6. *Case 3, M.M.* Surgically resected portion of stomach showing ulcer crater with surrounding ring of induration.

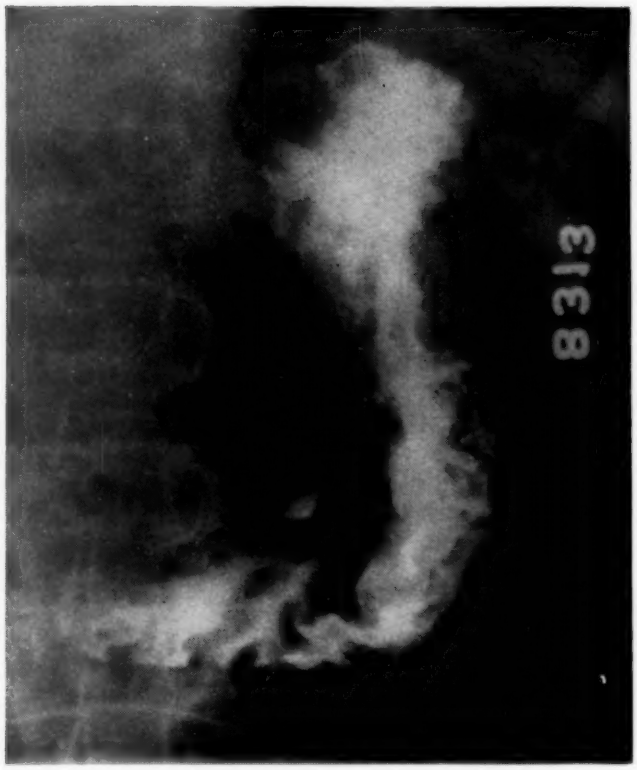

FIG. 7. *Case 4, L.I.* Barium contrast study of stomach showing large ulceration within an intraluminal mass.

FIG. 8. *Case 4, L.I.* Surgically resected portion of stomach showing large ulcer crater with surrounding thickened stomach wall.

TABLE 1

Summary of Cases

	Sex	Age	Duration of Symptoms	Presenting Symptom	Blood in Stool	X-Ray Findings	Diameter of Ulcer (surg. specimen)
Case 1, J. D.	M	66	Intermittent pain, 3 wks.; severe, intractable pain, 4 days*	Pain	+	Large gastric ulcer; induration of adjacent walls. Evidence of healed duodenal ulcer.	30 mm.
Case 2, I. E.	F	64	Intermittent pain, 1 mo.	Pain	−	Large gastric ulcer; induration of adjacent walls.	15 mm.
Case 3, M. M.	M	84	Vague mild heartburn, 2 mos.	Massive hemorrhage	+	Large gastric ulcer; induration of adjacent walls. No peristalsis.	16 mm.
Case 4, L. I.	M	65	Intermittent pain, 4 yrs.; wt. loss, 1 yr.; intractable pain and anorexia, 2 wks.†	Pain	+	Large gastric ulcer within an intraluminal mass; induration of adjacent walls. Evidence of healed duodenal ulcer.	25 mm.

* Duodenal ulcer two years previously.

† "Ulcer" twenty-five years previously.

scopic examination of many sections revealed the characteristics of chronic gastric ulcer. There was no evidence of malignancy.

DISCUSSION

The salient features of the 4 cases are presented in Table 1. Although 2 of the patients had a history of previous ulcer, the roentgenographic evidence indicated that these ulcers had been located in the duodenum. One of these 2 patients (Case 1, J. D.) had been free of symptoms for two years until three weeks before admission. The other one (Case 4, L. I.) had lost appetite and weight, and previously intermittent mild pain had become severe and intractable. In the other 2 cases, there had been no previous gastro-intestinal symptoms, and the histories were brief. In 3 of the 4 cases, the presenting symptom was pain; in the fourth, there was massive hemorrhage, manifested by hematemesis and melena. Stool samples contained blood in 3 patients. In all, x-ray study of the upper gastro-intestinal tract revealed large ulcer craters with surrounding induration.

Exploratory laparotomy was thought to be justified in view of the severity of the symptomatology. Moreover, the clinical findings in each patient were con-

sidered to be strongly suggestive of malignancy. Subtotal gastrectomies were performed, and in all 4 instances the ulcers were found to be benign.

Similar cases are frequently found in the literature on peptic ulcer. Mention is made by Bockus (1) of a large benign gastric ulcer in a female patient 71 years old. Here, too, the history was brief, the symptoms mild, and the x-ray findings suggestive of malignancy. Alvarez and McCarty (2), in a study of the sizes of benign and malignant gastric ulcerations, cited 2 cases in which the ulcer was more than 1,000 sq. mm. in area, in women 61 years old. In both cases the history was short and the preoperative impression was carcinoma. Sklar *et al.* (3) recently discussed gastro-intestinal disease in the aged and described 2 patients who were thought to have malignant lesions preoperatively, but actually had benign ulcers. According to a report by Smith *et al.* (4) on 578 surgically treated cases of gastric ulcer, 40.4 per cent of these ulcers were resected for suspected malignancy. Clinical and pathologic characteristics were not enumerated.

The generally accepted clinical criteria for benign gastric ulcer remain valid in most patients. The older patient, however, often presents an atypical clinical picture. Thus, the initial symptoms can be "unusual" and "vague" (5, 6), generally mild, or absent (7–11). A considerable number of patients may even be completely free of symptoms until a sudden severe complication such as massive hemorrhage or perforation occurs (9, 10). Gastric acidity is often normal or low (4, 8), as the secretory pattern changes in old age (12, 13). Frequently there is occult blood in the stool, but this finding is unreliable as a differential diagnostic feature (14).

The short history so characteristic of malignant ulcer (15, 16) is commonly observed in the benign ulcer of older people (10, 17). In addition, both the incidence and chronicity of benign gastric ulcer can be expected to rise with increasing age (4, 18). Even if the ulcer does not heal under medical management, this does not necessarily signify malignancy in the aged. There is little or no evidence for correlation between healing time and age of the patient, size of the ulcer, and recurrence or duration of symptoms (19, 20).

The size and location of gastric ulcers have been correlated with malignancy (2), but not with age or duration of symptoms. It is generally agreed that the larger the ulcer the greater the chance of malignancy, but the correlation may not be as strong in the older patient.

In general, then, older patients show far less correspondence between symptoms and laboratory and x-ray evidence than do younger patients. Although we have described only 4 cases, these and others mentioned in the current literature emphasize that large indurated ulcers in older patients are not as indicative of malignancy as has been supposed. In many such instances, therefore, x-ray examination alone may be insufficient for diagnosis (21), and co-existing classic findings of "malignancy" may incorrectly prejudice the interpreter in favor of carcinoma.

In view of the fact that many studies have shown an increasing incidence of severe complications of benign gastric ulcer and a sharp rise in mortality from

repeated massive hemorrhage and perforation in the older age group (7, 10, 17, 22–25), early definitive surgery should be considered more frequently, even when clinical and x-ray evidence seems to favor an infiltrating malignant condition.

SUMMARY

1. In patients over 60 years of age, large, indurated, adherent gastric ulcers suggestive of malignancy on x-ray examination are often not malignant.

2. These ulcers frequently have short clinical histories of mild symptoms and sudden exacerbations or complications such as intractable pain or massive hemorrhage.

3. Definitive surgical intervention should be attempted, in view of the markedly increased mortality from the complications of gastric ulcer in the older patient, and despite roentgenographic evidence suggestive of an infiltrative malignant lesion.

Acknowledgment

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REFERENCES

1. Bockus, H. L.: Gastroenterology. Philadelphia, W. B. Saunders Co., 1943, vol. 1.
2. Alvarez, W. C., and MacCarty, W. C.: Sizes of resected gastric ulcers and gastric carcinomas, *J. A. M. A.* **91:** 226–231, 1928.
3. Sklar, M.; Kirsner, J. B., and Palmer, W. L.: Gastrointestinal disease in the aged, *Med. Clin. North America* January, 1956, pp. 223–237.
4. Smith, F. H.; Boles, R. S., Jr., and Jordan, S. M.: Problem of the gastric ulcer reviewed; study of 1,000 cases, *J.A.M.A.* **153:** 1505–1508, 1953.
5. Rivers, A. B., and Dry, T. J.: Differentiation of benign and malignant gastric ulcer: unreliability of diagnostic criteria, *Arch. Surg.* **30:** 702–715, 1935.
6. Wood, M. N.: Chronic peptic ulcer in 94 diabetics, *Am. J. Digest. Dis.* **14:** 1–11, 1947.
7. Mulsow, F. W.: Peptic ulcer of the aged, *Am. J. Digest. Dis.* **8:** 112–114, 1941.
8. Meyer, J., and Saphir, O.: Peptic ulcer in the aged; clinical and postmortem study, *Am. J. Digest. Dis.* **10:** 28–30, 1943.
9. Boles, R. S., and Dunbar, W.: Peptic ulcer in old age, *Geriatrics* **1:** 217–225, 1946.
10. Lasher, E. P., Jr.: The course of peptic ulcer in elderly patients, *Surgery* **23:** 501–506, 1948.
11. Portis, S. A., and King, J. C.: The gastrointestinal tract in old age, *J.A.M.A.* **148:** 1073–1079, 1952.
12. Meyer, J. A., and Necheles, H.: Studies in old age. IV. The clinical significance of salivary, gastric and pancreatic secretion in the aged, *J.A.M.A.* **115:** 2050–2053, 1940.
13. Rafsky, H. A., and Weingarten, M.: A study of the gastric secretory response in the aged, *Gastroenterology* **8:** 348–352, 1947.
14. Walters, W.: Gastric ulcer, benign or malignant, *Arch. Surg.* **44:** 520–530, 1942.
15. Allen, A. W., and Welch, C. E.: Gastric ulcer, *Ann. Surg.* **114:** 498–509, 1941.
16. Welch, C. E., and Allen, A. W.: Carcinoma of the stomach, *New England J. Med.* **238:** 583–589, 1948.
17. Klingenstein, P.: Gastroduodenal ulcer in individuals more than 50 years of age, *J. Mt. Sinai Hosp.* **7:** 432–438, 1941.
18. Ivy, A. C.; Grossman, M. I., and Bachrach, W. H.: Peptic Ulcer. Philadelphia, Blakiston Co., 1950.

19. WHITE, F. W.: Observations on the healing of gastric ulcer, *New England J. Med.* **201:** 1075–1081, 1929.
20. CUMMINS, G. M., JR.; GROSSMAN, M. I., AND IVY, A. C.: A study of the time of "healing" of peptic ulcer in a series of 69 cases of duodenal and gastric ulcer, *Gastroenterology* **7:** 20–37, 1946.
21. JORDAN, S. M.: Gastric ulcer and cancer, *J. A. M. A.* **93:** 1642–1648, 1929.
22. DWYER, F. D.; BLACKFORD, J. M.; COLE, W. S., AND WILLIAMS, R. H.: Peptic ulcer: a review of 1033 cases and a follow-up study of the patients diagnosed between 10 and 20 years ago, *Radiology* **36:** 217–223, 1941.
23. GOLDMAN, L.: Gross hemorrhage from peptic ulcer; its morbidity, mortality and treatment, *J. A. M. A.* **107:** 1537–1542, 1936.
24. DEBAKEY, M.: Acute perforated gastroduodenal ulceration; statistical analysis and review of the literature, *Surgery* **8:** 852–884 and 1028–1076, 1940.
25. STOLTE, J. B.: Gross bleeding from digestive tract; frequency of manifest bleeding in peptic ulcer with regard to duration of the disease and to the age of the diseased, *Acta med. scandinav.* **116:** 584–593, 1944.

REVIEW OF DEATHS AND SOME MAJOR FEATURES OF INCAPACITY IN A TUBERCULOSIS HOSPITAL

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This institution became a tuberculosis hospital in November 1947, and since then the annual number of deaths has been decreasing. The average daily census for the years 1948 through 1955 was approximately 280. The number of deaths was as follows: 74 in 1948; 51 in 1949; 40 in 1950; 41 in 1951; 36 in 1952; 25 in 1953; 21 in 1954; and 18 in 1955.

The study covers a period of three years (1953, 1954 and 1955) during which there were 64 deaths. Autopsies were performed in 43 instances (67.2 per cent). All patients were males.

The distributions of these deaths as to the patient's *race and age* are shown for each year in Table 1. It is to be noted that in 1953, of all white patients dying, 53 per cent were over 45 years of age; in 1954, 64.3 per cent were over 45; and in 1955, the percentage had increased to 86.6 per cent. Of the Negroes dying in 1953, 60 per cent were over 45 years; in 1954, 57 per cent were over this age; but in 1955 none was over 45 years of age.

IMMEDIATE CAUSES OF DEATH

Year 1953

In 1953, 5 of the 25 deaths (20 per cent) were from hemoptysis. There were 4 deaths as follows: 1 from miliary tuberculosis with tuberculous meningitis; 1 from exfoliative dermatitis due to drug therapy given for far-advanced, rapidly progressing tuberculosis; 1 from luetic heart disease; and 1 from peritonitis following perforated peptic ulcer. Sixteen other deaths (64 per cent) were from uncomplicated pulmonary tuberculosis.

Year 1954

In 1954, 5 of the 21 deaths (23.8 per cent) were from hemoptysis. Five deaths were from the following causes: 1 from myocardial infarction from arteriosclerosis; 1 from Laennec's cirrhosis; 1 from miliary tuberculosis with tuberculous meningitis; 1 from spontaneous pneumothorax; and 1 from cardiovascular disease due to hypertension of the lesser circulation with cardiac enlargement and myocardial failure caused by long-standing pulmonary tuberculosis with extensive fibrosis (cor pulmonale). The remaining 11 deaths (52.4 per cent) were from uncomplicated pulmonary tuberculosis. The tuberculosis in 20 cases was active at the time of death; in only 1 case (the patient with cor pulmonale) had no acid-fast bacilli been found in the sputum for several years.

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TABLE 1

Distribution Regarding Race and Age of 64 Men Who Died from Tuberculosis

Year	Deaths—White Patients					Deaths—Negro Patients					Total Deaths All Races
	Under 45 yrs.	45–59 yrs.	Over 59 yrs.	Total white	Per cent of deaths (all races)	Under 45 yrs.	45–59 yrs.	Over 59 yrs.	Total Negro	Per cent of deaths (all races)	
1953	7	4	4	15	60	4	4	2	10	40	25
1954	5	4	5	14	67	3	2	2	7	33	21
1955	1	1	13	15	83	3	0	0	3	17	18
Total.....	13	9	22	44	68	10	6	4	20	32	64

Year 1955

In 1955, 3 of the 18 (16.7 per cent) deaths were due to hemoptysis. (One of these 3 patients died of a sudden massive hemorrhage a few hours after admission. His sputum was not examined, but a chest roentgenogram revealed an infiltrative lesion compatible with pulmonary tuberculosis.) Five patients (27.7 per cent) died of uncomplicated pulmonary tuberculosis. In 9 instances the immediate causes of death were as follows: 2 from myocardial infarction; 3 from cardiovascular disease due to hypertension of the lesser circulation (cor pulmonale); 1 from spontaneous pneumothorax; 1 from carcinoma of the lung with metastasis to the spine; 1 from cerebral hemorrhage; and 1 from cerebellar hemorrhage. Another patient was found dead in a hotel room while on a pass. Acid-fast bacilli had been present in the sputa of all but 3 of the 18 patients within the last two months of their lives. The 3 exceptions were as follows: a patient who died shortly after admission from a sudden massive hemorrhage; a patient with carcinoma of the lung and metastases to the spine; and a patient with spontaneous pneumothorax.

Of the 3 patients with cor pulmonale, 1 had had tuberculosis for thirty-five years, 1 for thirty-four years, and 1 for ten years.

Of the 18 patients who died, 3 were colored (aged 33, 35, and 37) and 15 were white. Of the 15 white patients, 13 were over 59 years of age, and the other 2 were 48 and 34 years of age. The oldest patient, a white man of 83 years, had acid-fast bacilli in his sputum; however, the cause of his death was a cerebellar hemorrhage.

Of the 3 patients dying from hemoptysis, 1 was a 35-year-old Negro who died in the afternoon of the day of admission; therefore he had not received chemotherapy or antibiotic therapy. One of the white patients, who died from hemoptysis was 34 years of age, and had active disease for eight years; he received streptomycin and para-aminosalicylic acid. The third patient was a 48-year-old white man who had been in the hospital for 752 days and was receiving isoniazid alone; after his initial hemoptysis he survived nine days, but continued to have small infrequent hemorrhages until his death.

In all but 1 of the proven cases of tuberculosis, the patient had received some

form of chemotherapy or antibiotic therapy at some time during the course of his disease. The exception was the man who died of massive hemorrhage on the day he was admitted. Two patients had not been given drugs for six months prior to death because of bacterial resistance to the medication; they had been treated by bed rest and the usual high-protein diet.

The patient with carcinoma of the lung received no antituberculosis drugs and the patient with spontaneous pneumothorax had received none in the recent period before death.

The 5 men who died of uncomplicated tuberculosis had a moderate to marked amount of emphysema, resulting from extensive long-standing chest disease. Longevity may have contributed to the emphysema (1, 2). If these patients had lived longer, cor pulmonale might have developed.

DISCUSSION

In view of the longevity of the 26 patients over 59 years of age at the time of death, it is apparent that the following factors may be of importance in the etiology of pulmonary distress:

1. Increased intrapulmonary pressure during strenuous coughing.
2. Secondary infections which result in extensive degenerative changes in the elastic elements of the lungs.
3. Partial bronchial occlusion of the check-valve type.

Griffith (3) states that "enlargement of the right ventricle is often a late sign in patients with cor pulmonale." He is of the opinion that in chronic pulmonary emphysema one should depend upon the presence of an accentuated pulmonary second sound and a forceful subxiphoid pulse with fatigability as the most important clinical diagnostic symptoms.

Dyspnea was the most common symptom in 13 of the 26 patients over 59 years of age who died. Dyspnea and fatigability are the most common complaints in our World War I veteran patients at the present time. Many now on the wards are almost wholly incapacitated by shortness of breath. On fluoroscopy the diaphragm is very low, the normal contour is lost and the excursions markedly limited. Abdominal belts alone, in our experience, have been of slight or no benefit. A few patients appear to obtain actual or psychologic relief by using aminophylline suppositories; the younger ones derive benefit from ephedrine and seconal capsules at bedtime.

Although it is true that the death rate from tuberculosis is falling rapidly, the number of cases of tuberculosis among older patients is increasing. This increase in the age of the average patient is very noticeable in the tuberculosis hospital or sanatorium (1).

The increase in age at the time of death appears to be chiefly confined to the white race.

The Negro possibly improves faster under chemotherapy than the white person, because of the more fulminating nature of his disease. The possibility has recently been voiced by Sweaney (4) that "in some acute and fulminating cases where all the bacilli are actively growing, there may be a complete steriliza-

tion of all bacilli present, as Steenken has reported in his animal experimentations."

With the increased life span of the consumptive, death frequently results from one of the many degenerative diseases of the aged, and not from tuberculosis per se.

Miller and Henderson (5) reported that significant and active tuberculosis was found approximately three times as often in persons over 40 as among those under 40. If emphysema, fibrosis or cor pulmonale be caused by tuberculosis, then it is reasonable to assume that at present tuberculosis in the aged presents a challenging problem, at least from the standpoint of prophylaxis of these three complications.

With the passing of time, the treatment of pulmonary tuberculosis may come largely within the province of the geriatrician or the general practitioner.

SUMMARY AND CONCLUSIONS

A review of deaths during the three-year period 1953 through 1955 in a 300-bed veterans' tuberculosis hospital has shown that the median age at death was 59 years for white males and 45 years for Negro males.

Deaths due to other causes, especially cardiovascular-renal diseases and malignancies, are a factor in reducing the death rate from pulmonary tuberculosis per se.

Longer periods of treatment for tuberculosis will be required in the future in association with increased longevity, especially among the white patients. This increased longevity also involves an increase in the number of patients severely handicapped by healing processes which limit pulmonary function and correspondingly restrict physical activity.

It is apparent that emphysema, pulmonary fibrosis and cor pulmonale are serious complications of pulmonary tuberculosis and should be made the targets of intensive study and research for control and alleviation.

REFERENCES

1. Shubin, H.: The preference for streptoduocin in the treatment of tuberculosis of the aging, *J. Am. Geriatrics Soc.* **4:** 65–69 (Jan.) 1956.
2. Motley, H. L.: Pulmonary emphysema; cardio-respiratory disturbance, *Dis. Chest* **29:** 292–304 (March) 1956.
3. Griffith, G. C.: Cor pulmonale: its diagnosis and management, *Dis. Chest* **29:** 258–265 (March) 1956.
4. Sweaney, H. C.: The overall effect of antimicrobial therapy on the tuberculosis program (Editorial), *Dis. Chest* **29:** 346–349 (March) 1956.
5. Miller, R. E., and Henderson, B.: Undiagnosed pulmonary tuberculosis in elderly persons, *Am. Rev. Tuberc.* **46:** 164–171 (Aug.) 1942.

TACE IN THE ENDOCRINE MANAGEMENT OF PROSTATIC CARCINOMA

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Chlorotrianisene (TACE*) is a unique estrogen with special properties which were first described by Thompson and Werner (1–3). It is active following oral administration, and its estrogenic effects are prolonged because of its distinct property of storage in the body fat. It is singularly free from effects upon the pituitary and adrenal, and does not cause the enlargement of these glands produced by comparable doses of other estrogens.

Since adrenal hyperplasia was thought to be a contributing factor in patients in whom there was a recurrence of prostatic cancer following long-term administration of estrogens, Smith, Rush and Evans (4) studied the effect of TACE in prostatic cancer. Their favorable clinical results were confirmed by other investigators (5–7).

CLINICAL MATERIAL

This report is concerned with 47 men treated for prostatic cancer with TACE during the past three years. Group I consists of 20 patients treated only with TACE for an average period of three years. Group II consists of 5 patients treated first with stilbestrol for an average period of eight months, and then with TACE for three years each, because they could not tolerate stilbestrol. Group II consists of 22 patients who had become resistant to stilbestrol. Twelve of this group have been under study for three years, and 10 have been under study for two years.

TACE was given to all patients in dosage of 12 mg. (one capsule) by mouth twice daily.

RESULTS

Group I. Of 20 previously untreated men with prostatic cancer, 15 are living comfortably at the end of three years, and 5 are dead. Three of the deaths were due to prostatic carcinoma, and 2 to causes other than cancer. The 20 patients ranged in age from 65 to 80 years. Orchidectomy was performed in only 5 cases, namely, those in which pain from bony metastases was no longer controlled by hormone therapy. There was little or no benefit from orchidectomy. Acid phosphatase levels were elevated in 11 of the 20 patients before treatment; 6 of these 11 are still living and the acid phosphatase levels are now within normal limits. In 6 of the 20 cases, bony metastases were present before treatment; mild regression of these lesions occurred in all 6 following treatment. In

* TACE is the trade-mark of The Wm. S. Merrell Company, Cincinnati, Ohio for its brand of chlorotrianisene.

5 others, bony metastases occurred during therapy. In all cases, the effect of TACE on the extension and nature of the primary lesion was prompt; however, in 9 of the 20 cases ultimately there was slow recurrence and extension.

Group II. Five men, ranging in age from 62 to 74 years, who were treated with diethylstilbestrol in a daily oral dosage of 5 mg., were found to be intolerant to this drug after a period of eight months. Intolerance was manifested by gastro-intestinal symptoms, severe tenderness of the breasts, and edema. TACE was substituted, in dosage of 24 mg. daily. It was well tolerated and there was a highly gratifying therapeutic response. Three years after the initiation of TACE therapy, 3 of these patients are living comfortably, and 2 are dead. At the beginning of TACE therapy, 2 patients had had bony metastases; in one there was objective evidence of improvement in these lesions, and in the other there was no change. Demonstrable metastases developed in another patient while receiving TACE.

Group III. Three years before the writing of this report, a group of 12 men who had become resistant to diethylstilbestrol in a daily dosage of 5 mg. to 15 mg. for periods of six to forty (average, twenty-nine) months, were given TACE instead in a dosage of 24 mg. daily. In these patients, further treatment with the commonly used estrogens would not be expected to bring about further response. Their ages ranged from 62 to 80 years (average, 69 years). After one year of TACE therapy, 2 patients were dramatically improved and 5 showed a moderately beneficial response varying from four to seven months in duration; 3 others had a mild degree of improvement for a period of three to five months; only 2 failed to improve. Encouraged by this initial response, we added 10 other stilbestrol-resistant patients to the series; making a total of 22.

Of the 12 men in this group who have been observed for three years, 2 are living and free from symptoms and 2 others are still alive but suffering pain from metastases. Of the 10 additional men who have been observed for two years, 6 have shown improvement in all respects, and 4 have had no benefit.

Acid phosphatase levels were elevated in 8 of the 22 patients at the time diethylstilbestrol was stopped and TACE was substituted. In 5 of these 8, the levels decreased to normal values during TACE therapy.

In patients who improved with TACE, there was a varying but sometimes pronounced degree of change in the primary tumors. In 4 cases, improvement in bony metastases was demonstrated. In only 2 of the 22 patients was orchidectomy performed, and in neither case did it enhance the effect of hormone treatment.

COMMENT

In our experience with prostatic cancer, the men who tolerate diethylstilbestrol well and obtain benefit generally continue to do well for about eighteen to twenty-four months. It appears that those who receive TACE generally do well for a longer period of time. The beneficial effects of TACE in patients who do not tolerate diethylstilbestrol or who no longer respond to it have been surprising. It has been proposed that the superiority of TACE in the endocrine management of prostatic carcinoma may be due in part to its freedom from effect upon

the pituitary and adrenal (4). An alternative hypothesis could be based upon the storage of TACE by fat in the body (1–3), and the gradual and constant release of estrogenic material, day and night, as soon as the body fat has been saturated with estrogen. Such saturation of human fat has been demonstrated by biopsy methods and reported by Greenblatt and Brown (8).

SUMMARY AND CONCLUSIONS

Chlorotrianisene (TACE) is a newer type of estrogen which is clinically useful in the endocrine management of prostatic carcinoma. In a series of 47 patients treated for a period of three years with a daily oral dosage of 24 mg., TACE appeared to produce a longer period of remission than would be expected with other estrogens, and it was frequently effective in patients no longer capable of responding to other estrogens.

REFERENCES

1. THOMPSON, C. R., AND WERNER, H. W.: A comparison of two synthetic estrogens, tri-*p*-anisyl chloroethylene and hexestrol, *Fed. Proc.* **41:** 137, 1945.
2. THOMPSON, C. R., AND WERNER, H. W.: Studies on the fate of tri-*p*-anisyl chloroethylene and hexestrol, *Fed. Proc.* **5:** 208, 1946.
3. THOMPSON, C. R., AND WERNER, H. W.: Studies on estrogen tri-*p*-anisylchloroethylene, *Proc. Soc. Exper. Biol. & Med.* **77:** 494–497 (July) 1951.
4. SMITH, P. G.; RUSH, T. W., AND EVANS, A. T.: Preliminary report on the clinical use of TACE (chlorotrianisene) in treatment of prostatic carcinoma, *J. Urol.* **65:** 886–889 (May) 1951.
5. O'CONOR, J. V., AND SOKOL, J. K.: Evaluation of TACE as a therapeutic agent in prostatic carcinoma, *Quart. Bull. Northwestern Univ. Med. Sch.* **26:** 161–162, 1952.
6. MORTENSEN, H.: The treatment of carcinoma of the prostate with a new estrogen, "TACE," *Med. J. Australia* **1:** 728–730 (May 23) 1953.
7. CARROLL, G., AND BRENNAN, R. V.: Endocrine therapy in carcinoma of the prostate, *J. A. M. A.* **157:** 581–583 (Feb. 12) 1955.
8. GREENBLATT, R. B., AND BROWN, N. H.: The storage of estrogen in human fat after estrogen administration, *Am. J. Obst. & Gynec.* **63:** 1361–1363 (Jan.) 1952.

Abstracts of Current Literature

REGULATIONSSTÖRUNGEN DES HIRNKREISLAUFS UND IHRE BEHANDLUNG (REGULATORY DISTURBANCES IN CEREBRAL BLOOD FLOW AND THEIR TREATMENT).

Bernsmeier, A. *Therap. Woche* **6:** 363, 1956; through Ciba Literature Review **1:** 237 (Aug.) 1956.

When organic vascular changes have occurred, as in arteriosclerosis and cerebral endangiitis, the cerebral blood flow is reduced. In such cases, the circulation cannot be increased by giving a single injection of a vasoactive substance, but it can be enhanced by prolonged therapy extending over several weeks. The author treated patients with cerebral endangiitis obliterans by administering 12 to 18 ampuls of Priscol (2-benzyl-4,5-imidazoline hydrochloride) by continuous drip infusion every other day. On the alternate days, the patients were given comparatively large doses of another vasodilator (usually Regitine). Thanks to these measures, the cerebral blood flow increased by about 60 per cent, the oxygen supply to the brain returned nearly to normal, and cerebral vascular resistance declined from 2.6 to 1.6 units while the arterial pressure remained unchanged. No conclusions could be drawn regarding the permanence of these improvements.

SURVIVAL OF DIABETIC PATIENTS AFTER MYOCARDIAL INFARCTION.

Bradley, R. F., and Bryfogle, J. W. *Am. J. Med.* **20:** 207 (Feb.) 1956; through Ciba Literature Review **1:** 234 (Aug.) 1956.

Almost 50 per cent of all patients with diabetes mellitus who have died in recent years succumbed to coronary artery disease. Examination of hospitalized diabetic patients has shown that disease of the coronary vessels is present in approximately 40 per cent. The prognosis for a diabetic patient with myocardial infarction is poor; 57.7 per cent of these patients who died from the first attack were diabetic subjects. Diabetes mellitus alone is sufficient to reduce the patient's life expectation sharply. This is particularly true of women, even though they may be suffering neither from angina pectoris, hypertension, obesity, nor heart failure, nor already have had a myocardial infarct. In male patients, on the other hand, the role of diabetes in early fatalities is less obvious. In diabetic patients with marked acidosis and hyperglycemia, a particularly early death is to be feared. By administering suitable treatment to diabetic patients, it is possible to reduce the incidence of lesions affecting the renal and ocular blood vessels as well as peripheral vascular lesions. It is uncertain, however, what effect treatment may have on the coronary vessels. In any case, it is unlikely that existing coronary artery damage can be repaired.

DIAGNOSE UND THERAPIE VASCULÄRER SEHSTÖRUNGEN (DIAGNOSIS AND THERAPY OF VASCULAR VISUAL DISTURBANCES).

Brückner, R. *Schweiz. med. Wchnschr.* **86:** 208, 1956; through Ciba Literature Review **1:** 238 (Aug.) 1956.

For acute retinal artery occlusion (usually caused by sclerosis, with and without hypertension, and less often by an embolism), the author recommends retrobulbar injection of one ampul of Priscol (2-benzyl-4,5-imidazoline hydrochloride). At the same time, Priscol eye drops are applied at ten-minute intervals or, alternatively, the eye is treated with Priscol ophthalmic ointment. Should the initial examination reveal that the blood flow in the retinal vessels has already come to a complete standstill, immediate intervention is essential, since this condition is still reversible if treated within the first half hour. This

emergency treatment can, if necessary, be administered by a general practitioner. One ampul of Pendiomide (N,N,N′,N′-3-pentamethyl-N-N′-diethyl-3-azapentylene-1,5-diammonium dibromide) is injected slowly intravenously over a period of ten minutes. Immediately afterwards, 1 to 2 ampuls of Ronicol (each 1 cc. ampul contains 50 mg. acetylchloride, 100 mg. β-pyridyl carbinol, and 1 mg. pyridostigmine bromide) or Niconazide are injected rapidly intravenously with the patient lying prone. If this treatment fails to restore retinal circulation, it is doubtful whether anything further can be accomplished by injecting acetylcholine into the corpus vitreum or by the classical method of puncturing the anterior chamber. In any case, once first aid therapy has been applied, there will be time to consider calmly what steps should be taken next. If the circulation is restored —which can easily be ascertained both subjectively and objectively—the patient must then undergo general treatment in the hospital with Liquaemin (heparin) therapy, heparin eye drops, iodine treatment, and the administration of vitamins. The patient's entire mode of living, including his work and rhythm of sleep, should also be subjected to careful hygienic control, and smoking forbidden.

BASES CLINIQUES ET PHYSIOPATHOLOGIQUES DU TRAITEMENT DES SYNDROMES OEDÉMATEUX PAR LA DELTA-CORTISONE (MÉTACORTANDRACINE) (CLINICAL AND PHYSIOPATHOLOGIC BASIS FOR THE TREATMENT OF EDEMATOUS SYNDROMES WITH DELTACORTISONE (METACORTANDRACIN)).

Cattan, R., and Vesin, P. *Sem. hôp. Paris* **32:** 712, 1956; through Ciba Literature Review **1:** 233 (Aug.) 1956.

Edema, whether of cardiac, renal or cirrhotic origin, is bound up with renal dysfunction, that is, with a diminution in filtration and an increase in the reabsorption of sodium, which is probably also accompanied by increased water reabsorption. When edema has developed, the excessive water and sodium cause a disturbance in the osmotic balance. This in turn provokes a rise in the secretion of sodium-retaining adrenal hormone (aldosterone) and of antidiuretic pituitary factors. A quantitative relationship has been established between the extent of edema on the one hand and the aldosterone level in the blood and urine on the other. Thus, the hormonal regulatory mechanisms are such that the edema "pays its own way" as it were. This vicious cycle can often be effectively interrupted by administering hormones of the cortisone type, especially prednisone. They inhibit the reabsorption of water in the renal tubules, the result being a marked increase in urinary excretion. Since prednisone corrects osmotic instability, it probably also causes a drop in the production of aldosterone. It has been noted that hormone therapy often enhances the effect of mercurial diuretics.

PAGET'S DISEASE OF BONE. INCIDENCE AND SUBCLINICAL FORMS.

Collins, D. H. *Lancet* **2:** 51 (July 14) 1956.

A detailed examination of the skeleton was made at 650 necropsies of unselected persons aged 40 or more. Pathological lesions of Paget's disease were discovered in 24 cases, an over-all incidence of 3.7 per cent. The result compares with Schmorl's (1932) figure of 3.0 per cent and confirms that Paget's disease, in some form, is very common in persons past middle life. Further data were compiled from 70 cases of Paget's disease studied pathologically. Paget's disease is exceptional in people aged less than 40 and uncommon in those aged 40 to 55 years. About 9 of every 10 cases of Paget's disease are found in persons aged at least 55 years. Cases were found in the incidence survey rather more frequently among women than among men, but this is not the general experience, and probably the sexes are affected in about the proportion of 4 men to 3 women. The common anatomical sites of Paget's disease are the lumbar vertebrae and sacrum, which seem to be affected in at least 3 of every 4 cases, and, after them, the skull and pelvic bones other than the sacrum. A solitary focus, affecting a single bone in whole or in part, may be the only lesion in about

10 per cent of cases. It does not necessarily mark an early stage in Paget's disease, for the pathological process in the solitary focus may be in a late stage of evolution. It merely represents a limited involvement of the skeleton. Paget's disease, though usually multifocal, is never diffuse. Of the 24 cases discovered during the incidence survey, only 1 patient had been admitted to the hospital as a direct consequence of Paget's disease (fracture of the cervical spine). Only 7 cases had been clinically or radiologically diagnosed as Paget's disease while the patients were in the hospital. Probably Paget's disease in 2 of every 3 cases remains throughout life in a subclinical form. In only about a third of all the cases are there physical signs or symptoms of Paget's disease that would lead to its detection in patients under medical care. In view of the frequency of Paget's disease among elderly persons and its prevalence in subclinical form, the incidence of fracture and sarcoma as complications has always been much overestimated. Special points in the pathological recognition of Paget's disease are described. (From author's summary and conclusions)

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE.

Frankel, A. N. *Am. J. Obst. & Gynec.* **72:** 131 (July) 1956.

Ten cases of primary carcinoma of the Fallopian tube are presented. These represented incidences of 1.6 and 0.43 per cent, respectively, among cases of primary carcinoma of the genital tract at the Beth Israel and Harlem Hospitals in New York during a ten-year period. The average age of the patients was 49 years. The most common complaints were vaginal discharge (two months to three years' duration) or bleeding, lower abdominal pain, and enlargement of the abdomen. The duration of pain was from two days to two years. Enlargement of the lower abdomen noted in 4 patients had been present from three months to fifteen years, and in 2 cases was associated with fibromyomas. A preoperative diagnosis was not made in this series. Pelvic malignancy was suspected in only 3 of the patients. One case was diagnosed at laparotomy and the others were discovered microscopically in the laboratory. Pathologic data are included. Operative procedures were performed as follows: total abdominal hysterectomy and bilateral salpingo-oophorectomy, 5; supracervical hysterectomy and bilateral salpingo-oophorectomy, 4; and left salpingo-oophorectomy with vaginal draining for pelvic abscess, 1. The five-year survival rate was 10 per cent, as 1 patient lived eight years and at the end of that time was learned to have carcinoma of the cervix. One patient is alive and well three and a half years postoperatively. Metastases developed in the remaining patients, but they were known to have lived from fifteen months to four years postoperatively. Primary carcinoma of the Fallopian tubes is difficult to diagnose. Papanicolaou vaginal smears examined routinely in cases of vaginal discharge or bleeding may be an aid to early diagnosis, provided the isthmic portion of the tube is patent. The low salvage rate might be raised if the clinician were cognizant of the possibility of primary carcinoma of the Fallopian tube, if Papanicolaou vaginal smears were used routinely in cases of vaginal discharge or bleeding, and if an exploratory laparotomy were performed for all adnexal masses which after careful investigation cannot be accurately diagnosed or of which the diagnosis is still in doubt.

INTÉRÊT PRATIQUE DE LA RECHERCHE DE LA PROTÉINE C (PRACTICAL INTEREST IN RESEARCH WITH REGARD TO PROTEIN C).

Gautier, A. *Med. et hyg.* **14:** 261, 1956; through Ciba Literature Review **1:** 222 (Aug.) 1956.

Protein C occurs in the blood serum whenever inflammation, necrosis, or a tumor are present. It is not an antibody, since it is completely nonspecific. As regards its chemical composition, electrophoresis has shown that it occupies a position between α2-globulin and β-globulin. The quantity of protein C present is extremely small, amounting to only about 0.2 per cent of the total serum proteins. Its presence can be demonstrated by precipitation, using a special rabbit serum. Of particular significance is the fact that protein C

appears in the early stages of a disease; it disappears towards the end of the acute phase. For this reason, it affords a suitable means by which to determine the degree of inflammation or the extent of necrosis. It is often possible to detect protein C in the blood serum before the erythrocyte sedimentation rate has increased. Protein C is also a valuable aid in the differential diagnosis between myocardial infarction (protein C test always present) and angina pectoris (protein C absent). In rheumatic fever, the protein C test provides a more accurate guide to the activity of the disease than the erythrocyte sedimentation rate; the latter may, for example, increase at the end of treatment although there may be no relapse, whereas the results of the protein C test remain negative. Hormonal therapy as such does not bring about the disappearance of protein C; it is only when the inflammatory process has become inactive that protein C disappears.

HUMAN ARTERIAL HYPERTENSION: A STATE OF MILD CHRONIC HYPERALDOSTERONISM?

Genest, J.; Lemieux, G.; Davignon, A.; Koiw, E.; Nowaczynski, W., and Steyermark, P. *Science* **123:** 503 (March 23) 1956; through Ciba Literature Review **1:** 232 (Aug.) 1956.

The urinary excretion of aldosterone was studied in patients suffering from either malignant hypertension or severe essential hypertension. The method of determination used was by injection into adrenalectomized rats. It was found that hypertensive patients excrete relatively large quantities of aldosterone. Two characteristic signs of the effect of aldosterone were evident in both groups of patients, that is, a decrease in total sodium excretion and a fall in the sodium/potassium ratio. This increased output of aldosterone might possibly explain the abnormalities of sodium metabolism observed in hypertensive subjects and the occurrence of hypertension in cases of adrenal hypercortisonism. Conceivably, human arterial hypertension might be caused by a state of mild and chronic hyperaldosteronism.

ACUTE LEUKEMIA OVER THE AGE OF FIFTY: A STUDY OF ITS INCIDENCE AND NATURAL HISTORY.

Gunz, F. W., and Hough, R. F. *Blood* **11:** 882 (Oct.) 1956.

An analysis is presented of all deaths in New Zealand in a five-year period, certified as having resulted from leukemia. As in other parts of the world, the incidence of leukemia proved to be highest in older age groups. The incidence rose sharply above age 50 years, which seems to be in accord with a comparatively recent trend noted elsewhere. Acute forms accounted for a notable part of the leukemia in this age group. Ninety-seven case records were studied in detail in order to detect any differences between the manifestations of acute leukemia in middle-aged and elderly people. The clinical, hematologic, and pathologic findings in acute and chronic leukemia in persons past 50 years of age are given. The outstanding findings in patients over age 50 years with acute leukemia were: 1) Their early history closely mimicked that of chronic leukemia both in duration and nature of symptoms. Thereafter (with the diagnosis established) the course of the disease was sharply different, in that death usually occurred within six weeks. Although the insidious onset of acute leukemia in these patients resembled that of chronic leukemia, it contrasted vividly with that in most cases of acute leukemia in young patients. 2) Abnormal physical signs were scarce in comparison with the chronic group, and probably also with children and young adults with acute leukemia. 3) The disease was resistant to most forms of therapy. This is unlike the earlier phases of chronic leukemia and differentiates these patients from younger ones with acute leukemia. Agreement is practically unanimous among workers in this field that few remissions are produced in adults by the same therapeutic agents which may be highly successful in children with acute leukemia. 4) Hematologic and histologic findings in different patients varied widely and lacked correlation with the length or

nature of the clinical history. These features serve to distinguish this type of leukemia from chronic leukemia and from acute leukemia in young patients. Because of its usually brief clinical course following diagnosis, its intractability, and the generally high degree of immaturity of the pathologic leukocytes, it should be termed "acute," whatever the length of indefinite symptoms prior to diagnosis. Inasmuch as the pathologic process which leads to the development of this fatal disease is not known, it cannot be determined whether it is the same as, or differs from that which leads to acute leukemia at earlier ages. The frequency of its occurrence makes it highly desirable to concentrate further research on its clinical features, pathologic background, and especially on a means of treating it successfully.

DIAGNOSE UND BEHANDLUNG DER FUNKTIONELLEN HARNINKONTINENZ (DIAGNOSIS AND TREATMENT OF FUNCTIONAL INCONTINENCE OF URINE).

Hartl, H. *Gynaecologia* **141:** 375, 1956; through Ciba Literature Review **1:** 242 (Aug.) 1956.

Hartl describes three modern methods of examination for the diagnosis of functional incontinence of urine: sphincterometry, cystometry, and urethrocystography. Sphincterometry involves measurement of the pressure required to open the sphincter of the bladder. In cystometry, the intravesical pressure is graphically recorded while the bladder is being filled. This method provides evidence concerning changes in the stimulus threshold, bladder capacity, and intravesical pressure, as well as indicating the degree of efficiency of the detrusor urinae. With the aid of urethrocystography, it is possible to assess the functioning of the tissues surrounding and supporting the bladder and of the pelvic floor in response to loading, and the efficiency of the closing mechanism of the sphincteral system.

A NEW 4-OXYCOUMARIN DERIVATIVE, G-23350 (SINTROM).

Long, L. A.; Colpron, G., and Marion, P. *Canad. M.A.J.* **75:** 261 (Aug. 15) 1956.

The ideal anticoagulant should lower prothrombin concentration to a therapeutic level in a minimum of time, maintain prothrombin at the therapeutic level until the subsequent dose, permit the return of the prothrombin to normal concentration as soon as possible after cessation of treatment, and be well tolerated and nontoxic. The new anticoagulant, Sintrom, has proved superior in these respects to several other synthetic drugs. In therapeutic dosage, Sintrom is 50 to 100 times as effective as Tromexan. Sintrom was used in the treatment of 92 patients with cardiovascular disorders. In 50 patients, the daily concentrations of prothrombin, proconvertin, and proaccelerin were determined. The remaining 42 patients received daily dosages of Sintrom in accordance with the daily prothrombin level determined by the so-called "bedside" technic. Treatment was continued from seven to sixty days and for one hundred and twenty-one days in 1 patient. Following their discharge from the hospital, 4 patients were maintained on Sintrom for more than one year. The maintenance dosage having been established, only a weekly prothrombin determination was necessary to check the maintenance of prothrombinemia at a therapeutic level. The initial dose of Sintrom varied from 16 to 24 mg., and occasionally was 24 mg. The maintenance dosage averaged 5 mg. per day. The effective therapeutic prothrombin concentration could be reached rapidly. Return to normal occurred between twenty-four and seventy-two hours after cessation of treatment, its ready restoration to normal representing an advantage of Sintrom. Several instances of hemorrhage occurred during the study but responded rapidly to the administration of vitamin K. In addition to possessing rapid action and relative stability of effect, Sintrom in therapeutic doses is nontoxic and safe. The stability of its action eliminates the danger of formation of emboli. The integrity of hepatic function should be verified before undertaking anticoagulant therapy with this and other coumarin derivatives. In hepatic insufficiency, only minimal doses of anticoagulant are necessary to maintain a therapeutic hypoprothrombinemia.

WIRKUNG VON ADELPHAN AUF DIE ARTERIELLE STROMBAHN (EFFECT OF ADELPHAN ON THE ARTERIAL PASSAGEWAY).

Lühr, L. *Ztschr. f. Kreislaufforsch.* **45:** 321, 1956; through Ciba Literature Review **1:** 229 (Aug.) 1956.

Lühr studied at regular intervals the hemodynamic effects of Adelphan (0.1 mg. of Serpasil with 10 mg. of 1,4-dihydrovinophthalazine per tablet) in patients with severe hypertension. Following a preparatory period of three weeks, the drug was administered in daily dosages of three to four tablets. The heart rate slowed by an average of 12 beats per minute. As the minute volume remained practically unaltered, a relative increase took place in the stroke volume. The mean blood pressure (the arithmetic mean of the systolic and diastolic pressures) declined on an average from 170.5 to 142 mm.Hg. A reduction of 15.5 mm. Hg was recorded in the first five days. The pulse wave velocity dropped from 10.1 to 8.75 m. per second, and the basic oscillations of the pulse wave in the femoral artery were considerably prolonged. Both these findings indicate that Adelphan produces a clear-cut reduction in the elastic resistance of the blood vessels. The author concludes that Adelphan is an effective drug, and one that not only lowers blood pressure but also exerts a beneficial effect on other factors involved in hypertension. No side-effects or unpleasant consequences of this hemodynamic readjustment need be feared.

RUPTURE OF THE HEART AFTER MYOCARDIAL INFARCTION.

Maher, J. F.; Mallory, K., and Laurenz, G. A. *New England J. Med.* **255:** 1 (July 5), 1956.

The frequency of occurrence of cardiac rupture as a complication of myocardial infarction suggested the possibility that newly introduced methods of therapy favor cardiorrhexis. The literature on rupture of the heart is briefly reviewed. Twenty-one cases of cardiac rupture among 183 recent myocardial infarcts were analyzed. These infarctions were observed during 1,928 routine necropsies. The incidence of rupture was 11.8 per cent of recent myocardial infarctions and 1.1 per cent of all necropsies. Two of the cases were of septal rupture, 1 of them being diagnosed ante mortem. The incidence of cardiac rupture was found to be lower among patients who manifested an old infarction at necropsy or congestive heart failure clinically, or were treated with diuretics, antibiotics or maintenance digitalis therapy. The incidence was greater in association with hypertension and exertion. The increased frequency of cardiac rupture in association with shock, the use of Levarterenol or anticoagulants, or the armchair treatment of myocardial infarction was not significant. The results of this study are in accord with those of other recent studies. In view of the incidence of cardiac rupture it should not be considered rare. Prevention appears to be the only solution to cardiac rupture. Rest during the period immediately following infarction should be emphasized. Patients with hypertension and those without evidence of heart failure, in particular, should be kept at rest in order to prevent rupture.

ACTH, CORTISONE ET TUBERCULOSE (ACTH, CORTISONE AND TUBERCULOSIS).

Moreau, L. *Concours med.* **78:** 1813, 1956; through Ciba Literature Review **1:** 216 (Aug.) 1956.

With regard to the long-disputed question whether it is permissible to treat tuberculosis with ACTH or cortisone, experience to date indicates that, provided they are used in the correct indication, these hormones are useful in patients suffering from tuberculosis. It is important to avoid too high a dosage, and at the same time to apply energetic antibacterial therapy with isoniazid, streptomycin, or similar agents, and to proceed with caution. ACTH and cortisone often bring about a decisive change for the better, especially in patients with a poor prognosis. They have even yielded astonishingly good responses in instances in which antibiotics had been either without effect or badly tolerated. On repeated occasions, ACTH or cortisone has overcome both these snags. These two hormones are particularly

indicated in severe and rapidly progressive pulmonary tuberculosis, in cases with purulent effusion, and in tuberculosis of the serous membranes, accompanied by violent inflammatory symptoms, high temperature and a marked deterioration in the patient's general condition.

COUMADIN (WARFARIN) SODIUM. A NEW ANTICOAGULANT.

Nicholson, J. H., and Leavitt, T., Jr. *New England J. Med.* **255:** 491 (Sept. 13) 1956.

Coumadin sodium is a stable monocoumarin compound that forms stable aqueous solutions. The literature on the substance is reviewed and two years' experience with its use in 100 patients is reported. The following thromboembolic conditions were present in the numbers of patients indicated: acute myocardial infarction and intermediate coronary artery disease, 61; pulmonary embolism, 15; thrombophlebitis of lower extremities, acute, 18; arterial emboli, 3; and cardiac disease, 3. The initial dose of coumadin sodium averaged 60 mg. Maintenance doses were administered by an intermittent or continuous dosage schedule, based on daily prothrombin determinations, and averaged 10 mg. The maintenance dosage proved relatively constant for each patient. The drug was administered intravenously at first and then orally, there being no essential difference between the two modes of administration. Therapeutic hypoprothrombinemia (a level of 35 to 10 per cent) could be induced promptly. All patients responded by a lowering of prothrombin concentration to the stated range within forty-eight hours. The time required to return to normal after cessation of therapy was not determined because maintenance therapy was instituted; but examples of five, eight, and nine days' duration of effect after the initial dose were observed. The length of therapeutic effect appeared to be related to early onset. Compared with Tromexan, coumadin sodium induced a hypoprothrombinemic effect as quickly, but the prothrombin-inducing action was more prolonged and more stable. Fewer periods of "escape" from the therapeutic range occurred than with other anticoagulant drugs used, particularly with the continuous method of maintenance therapy. Based on the results of long-term therapy in 4 patients, the maintenance dose appeared to be easier to control than that of Dicumarol. Hemorrhage responded in 3 patients postoperatively, and levels of prothrombin below 10 per cent in 3 other patients were elevated, when vitamin K was administered. Withholding the drug for several days caused petechiae to disappear in 2 patients. No toxic side-effects were noted. During therapy, no patient had pulmonary embolism, thrombophlebitis, or arterial embolism not existing prior to the administration of coumadin sodium. This drug is concluded to be a more nearly ideal anticoagulant than any of the coumarin derivatives now available, and to deserve wide clinical application in thrombotic and thromboembolic disorders.

VALORE DEL BILANCIO AZOTATO NEL PAZIENTE CHIRURGICO DI ETÀ AVANZATA (EVALUATION OF THE NITROGEN BALANCE IN SURGICAL PATIENTS OF ADVANCED AGE).

Occhipinti, S., and Japichino, G. *Minerva med.* **47:** 1556, 1906; through Ciba Literature Review **1:** 236 (Aug.) 1956.

In elderly subjects who are suffering from illness or have undergone a major operation, the nitrogen balance frequently is negative. This involves risks of shock, delayed healing of wounds, reduced immunity, and alterations in the biologic regulatory mechanisms of the organism—all of which are liable to occur in patients at any age. However, in geriatric patients, these changes tend to be more severe and prolonged, and are also more difficult to overcome. Studies conducted on patients over the age of 60 years have shown that daily administration of 1 Gm. of protein per kilogram of body weight is sufficient to maintain a positive nitrogen balance, provided the loss of energy be compensated by an adequate supply of calories. It is difficult, however, to provide the patient with sufficient protein parenterally. The surgeon, therefore, should make a thorough investigation of the patient's protein balance and do his utmost to see that it is correctly adjusted before proceeding to operate.

THE HYDROGENATED ALKALOIDS OF ERGOT (HYDERGINE) IN GERIATRICS—FOLLOW UP STUDY.

Popkin, R. J. *Am. Pract. & Digest. Treat.* **7:** 1594 (Oct.) 1956.

This is a follow-up report on the use of Hydergine (a mixture of hydrogenated alkaloids of ergot: dihydroergocornine, dihydroergocristine, and dihydroergokryptine) in the management of 400 geriatric patients. Many were under treatment simultaneously for such illnesses as arteriosclerosis obliterans, coronary artery disease, hypertension, cerebrovascular accidents, arthritis, chronic thrombophlebitis, cerebral arteriosclerosis, genitourinary conditions, and malignancy. The effective dosage was 2 to 4 sublingual tablets daily. Each tablet contained 0.5 mg. of active substance. Pharmacologically, Hydergine affects the central nervous system, inhibiting sympathetic activity, with a reduction in vessel tone. It also possesses a latent peripheral sympathetic effect. All of the patients had been under observation for many years, so that their responses to drugs and their general course with exacerbations and remissions were known. Subjective and objective signs of improvement were sufficient to justify a favorable evaluation of the drug. Patients experienced improvement in well being and became easier to manage. They seemed to be eased into advancing age with less disability and fewer complaints. The best results were obtained with prolonged therapy. Improvement occurred in stamina, walking ability, ability to adjust, and in cerebral symptoms such as dizziness, headaches, undue fatigue, memory loss, increased irritability, inability to concentrate, and apathy. Objective signs of improvement included increased surface temperatures and oscillometric readings of the extremities, increased healing of venous and arteriosclerotic ulcers, easier and more adequate control of dependent edema, lessening of periods of disability following arthritis and disorders of locomotion, more rapid recovery from disabling and degenerative diseases, decrease in residual symptoms of cerebrovascular accidents, decrease in incidence and extent of gangrene from occlusive arterial disease, and less likelihood to succumb to repeated coronary occlusions or cerebrovascular accidents. Hydergine was well tolerated and unusually well accepted by elderly patients. Its use was continued for years by patients who ordinarily would be expected to rebel against continuous medication.

FRACTURE OF THE FEMORAL NECK FOLLOWING IRRADIATION OF THE PELVIS.

Ralston, E. L. *Surg., Gynec. & Obst.* **103:** 62 (July) 1956.

Fracture of the femoral neck occurs in 1 to 2 per cent of cases undergoing pelvic irradiation for carcinoma. Optimum results in treatment can be attained only if this complication is recognized and diagnosed early. It should be suspected in all patients who complain of pain in the hip or knee following irradiation for pelvic carcinoma. Early roentgenograms commonly fail to show this fracture but it may be seen after a few weeks. When weight-bearing has been prevented, deformity is unlikely and internal fixation can be accomplished with successful union in most cases. Optimum results cannot be achieved with a delay in diagnosis. Delay in diagnosis has resulted in necrosis of the femoral head with results less than satisfactory. If necrosis of the femoral head has occurred, a femoral head prosthesis will be required. The total amount of irradiation received appears to be a factor in the occurrence of complete necrosis of the head. The tolerance dose of the femoral head and neck has been ascertained as 3,840 to 4,320 roentgens. The exact effect of roentgen irradiation of bone is not understood. The pathologic changes in fracture of the femoral neck have been described and are reviewed briefly. Four case reports are given.

CEREBRAL ARTERIOSCLEROSIS. SURVEY OF 500 PSYCHOTIC PATIENTS WITH CEREBRAL ARTERIOSCLEROSIS.

Raskin, N., and Ehreberg, R. *Am. Pract. & Digest. Treat.* **7:** 1095 (July) 1956.

This survey was based on an analysis of the clinical records of, and necropsy findings in, 500 psychotic patients between the ages of 60 and 97 years with cerebral arteriosclerosis.

A comparison of findings in these patients with those in normal elderly people indicated that psychosis in an elderly person is not necessarily due to his arteriosclerosis. No difference was found in the character, localization, or extent of brain lesions between normal and psychotic arteriosclerotic persons. The psychotic reactions described as a result of cerebral arteriosclerosis may be precipitated by the toxic effects of alcohol, malnutrition, hypoxia due to cardiac decompensation, or emotional factors. The histories of these elderly patients with cerebral arteriosclerosis showed that many could lead fairly normal lives at home with the sympathetic assistance of their families and physician until some sudden unwelcome change in the established order of living caused increased anxiety or insecurity, or a stroke. The psychotic status in cerebral arteriosclerosis seemed to depend upon the patient's prepsychotic personality. The emotional reaction appeared to be the starting point for their psychosis. Many of these patients can make a good recovery, despite arteriosclerotic lesions, with good medical care, improved diet, increased fluid intake, attention to bowels, adequate vitamin intake and, in some cases, electric shock treatments. This study indicates that with preventive and curative treatment it may be possible to reduce the number of elderly people with cerebral arteriosclerosis in need of mental hospital care.

DIE DIAGNOSTISCHE BEDEUTUNG DER PERCUTANEN SPLENO-PORTOGRAPHIE (THE DIAGNOSTIC SIGNIFICANCE OF PERCUTANEOUS SPLENO-PORTOGRAPHY).

Róth, M., and Jóna, J. *Schweiz. med. Wschnschr.* **86:** 738, 1956; through Ciba Literature Review **1:** 242 (Aug.) 1956.

With percutaneous spleno-portography, it is possible to make a differential diagnosis between the various types of portal hypertension (prehepatic, intrahepatic and posthepatic forms). In the majority of cases, an exact diagnosis based on the results of this procedure affords the only reliable guide to the choice of surgical treatment. Spleno-portography is also a useful aid in ascertaining the site of hepatic and pancreatic tumors.

LEBENSAUSSICHTEN VON ESSENTIELLEN HYPERTONIKERN BEI JAHRELANG EINGEHALTENER SALZFREIER DIAT (LIFE EXPECTANCY IN ESSENTIAL HYPERTENSION WITH PROLONGED USE OF A SALT-FREE DIET).

Sarre, H.; Kampmann, W., and Schmidt, G. *Klin. Wchnschr.* **34:** 509, 1956; through Ciba Literature Review **1:** 231 (Aug.) 1956.

The study was designed to shed light on the question of the influence of a low-salt diet on hypertension, that is, on the patient's life expectation and the cause of death. Forty-five patients living on a strict "saltless" diet for periods up to nine years were compared with 45 control patients with similar histories, blood pressures, eyegrounds, and complications. The diet had a beneficial effect during the first three years. Although fewer of the patients living on the diet died in the first to third years of observation, this lower mortality rate was cancelled out in the fourth and fifth years, with the result that the number of survivors in the sixth to ninth years was the same for both groups. It would appear that dietary restriction of salt intake can affect the course of essential hypertension for only a few years. Its beneficial effect is most apparent in severe cases. Death from heart failure tended to occur later in the patients who received the diet than in the control group. Death from apoplexy was also deferred by two to three years. It is clear that in the long run a "saltless" diet cannot fulfill the expectations which short-term observation would at first appear to justify. On the other hand, in serious cases of cardiac decompensation, it may help to prolong the patient's life by several years.

ANEURYSM OF THE ABDOMINAL AORTA AND ILIAC ARTERIES.

Wheelock, F., and Shaw, R. S. *New England J. Med.* **255:** 72 (July 12) 1956.

Twenty-one abdominal aneurysms were treated by resection and replacement with homologous artery grafts. Two were in the common iliac artery and the remainder involved the lower abdominal aorta. All patients with aortic aneurysms noted pain in the abdomen

or back and an obvious pulsating mass was present in the upper abdomen. Elective operations were performed in 14 of the aortic cases, but 5 aortic and the 2 iliac aneurysms required emergency surgery because of rupture. The operative technic is described and the etiology, pathology, symptoms and signs, roentgenographic study, and natural history of aneurysms are discussed. In unruptured cases, spinal anesthesia with the agent instilled through a catheter is the anesthesia of choice, because good relaxation is obtained and the technic allows the blood pressure to be lowered. In the case of rupture, anesthesia may have to be accomplished more rapidly and be of a type not to disturb a poorly compensated low blood volume. A long midline or left paramedian incision usually provides adequate exposure. Arteriosclerosis of the aorta did not prevent making a satisfactory anastomosis in patients in this series. No patient having elective surgery died at or following the operation, and all except 2 were alive upon follow-up one to twenty-eight months later. The 2 patients who died at one month and at two years did so from other causes. At necropsy, the first graft appeared unchanged except for fibrous tissue organization. The two-year graft showed transverse folds but no tendency towards aneurysm. In the living patients at last visit, there was no evidence of disorder in the graft. Three among the 7 patients with ruptured aneurysms died. Anuria or severe oliguria contributed to these deaths and 2 patients showed evidence of recent myocardial infarction at necropsy. The other 4 patients are alive and well after postoperative periods of seven months to two years. Resection of abdominal aneurysms and arterial grafting are concluded to remove the danger of death from rupture. These operations can be performed with reasonable operative mortality. However, if rupture has occurred, few patients can be saved. Surgery is indicated in a patient with an abdominal aneurysm if his general condition is reasonably good. Resection and graft should be considered even in poor-risk patients if the aneurysm is large or symptomatic, because of the great danger of rupture under these circumstances. However, it is better to let small asymptomatic aneurysms remain untouched if associated disease or great age makes the operative risk grave or the prognosis poor.

UEBER DIE ANWENDUNG VON SERPASIL BEI DER BEHANDLUNG VON HAUTKRANKHEITEN. VORLÄUFIGE MITTEILUNG (THE USE OF SERPASIL IN THE TREATMENT OF DISEASES OF THE SKIN. PRELIMINARY COMMUNICATION).

Wolfram, St. *Hautarzt.* **7:** 183, 1956; through Ciba Literature Review **1:** 235 (Aug.) 1956.

Serpasil exerts a beneficial effect on various skin diseases by alleviating itching. Patients with pruritus senilis generally reacted well, whereas those with pruritus ani and vulvae varied in their response. In the latter indication, Serpasil is mainly useful for restricting the use of barbiturates. Serpasil has little effect on pruritus of allergic origin. In patients with psoriasis vulgaris, a combination of local therapy and Serpasil yielded better results in 50 per cent of cases than local treatment alone. In chronic recrudescent urticaria, Serpasil alleviated itching and had a favorable influence on the eruptions. Particularly encouraging responses were observed in cases in which psychic factors were involved. Clear-cut improvement occurred in 16 of 20 patients with neurodermatitis. Of 40 patients with eczema, 30 obtained marked relief from itching, the vicious cycle of eczema aggravated by itching thus being overcome. Serpasil was given in doses up to 1 mg. three times daily. As a rule, improvement began after about one week of treatment. Such side-effects as occurred were slight. Only in 3 of a total of 113 patients was it necessary to withdraw the drug because of the drop in blood pressure and the tendency to collapse which it had produced. In normotensive subjects, no fall in blood pressure was observed. The sedative effect which Serpasil sometimes exerted also proved beneficial.

CONSTIPATION IN THE AGED.

Zimmerman, K. *Pennsylvania M.J.* **59:** 1158 (Sept.) 1956.

Constipation may be no more prevalent among elderly persons than among those of middle age, but the degree seems to be greater. Factors that may be related to constipation

in elderly people are: decreased food intake, water intake, and physical activity; atonic intestinal muscle; a high incidence of anorectal disorders; and a long-standing cathartic habit. A careful history will reveal the status of the intake of water and of bulk, the presence of anorectal disorders, and the cathartic habit. Loss of tone in the intestinal wall can only be determined by a proctoscopic examination. A recent change in bowel habit is an early sign of cancer and calls for a sigmoidoscopic examination and barium enema. Besides dietary corrections, mineral oil or dioxyl sodium sulfosuccinate, a wetting agent, will prove helpful and keep the stool soft. If physical activity cannot be increased, a certain degree of relief may be obtained by massaging the abdomen. Anorectal disorders should be corrected, if possible. When a rectocele in an elderly woman cannot be corrected surgically, pressure against the posterior vaginal wall while the bowels are moving will assist in emptying the rectum. For the patient with the cathartic habit, a combination of training, diet, instruction, and various aids is usually required. The stool may be kept soft by using bulk-forming material, oil, or a wetting agent. A warning is given against the use of bulk laxatives in elderly people who will not increase the intake of water; there is danger of impaction. Small plain-water enemas may initiate the desire for a bowel movement. Salines taken before breakfast may be used to replace irritants if the patient drinks a large quantity of water. Sometimes the irritant will have to be continued because results cannot be obtained without it. An attempt to cure a patient of a cathartic habit of many years' duration is impractical. The physician's obligation is fulfilled if he achieves relief from constipation that causes no harm and is not too inconvenient.

NEWS AND NOTICES

ANNOUNCEMENT OF CLINICAL INVESTIGATOR PROGRAM, VETERANS ADMINISTRATION, WASHINGTON 25, D. C.

Purpose. The needs of the Veterans Administration Medical Program and the potential of its research and education activities in contributing to the health of the nation are such that it is planned to train selected physicians and dentists whose primary responsibility will be medical research. The candidates for this appointment must be interested in problems of particular importance in the care of veteran patients in fields basic to neurology and psychiatry, cardiovascular disease, cancer, degenerative diseases, and problems involving the aging process. Maximum freedom of choice of subject will be allowed within these broad fields.

Eligibility. Any physician or dentist who has completed at least the formal residency training period required prior to American Specialty Board certification and because of special interest and aptitude wishes to do full-time research for a period of possibly up to three years.

General plan. The Clinical Investigator will spend at least three-fourths of his time in research. The balance of his time may be spent in teaching and patient care or in whatever professional activity he and his sponsors agree is advantageous for his development. He will be appointed as a full-time member of the Veterans Administration hospital staff and his official title will be Veterans Administration Clinical Investigator. He will be entitled to the privileges and benefits of other full-time physicians and dentists such as insurance and retirement eligibility, annual and sick leave. All Clinical Investigators will have research as their primary responsibility; they will, in addition, hold suitable clinical appointments on the hospital staff which will enable them to enjoy the privileges of a responsible relationship to the patient care program.

Salary. The Clinical Investigator will be appointed at Intermediate Grade. The beginning salary is $8,990 per annum. Additional credit will be given for American Specialty Board certification in accordance with existing regulations.

Nomination and selection. Candidates are nominated to the Veterans Administration hospital manager through the Veterans Administration Hospital Research Committee for approval by the Deans Committee. From the group of nominees the Clinical Investigators will be selected by the Central Advisory Committee composed of outstanding educators and investigators.

Form of application. The candidate should submit a curriculum vitae, including transcripts of his scholastic record and any other information which might help the Committee in its evaluation. He should prepare a detailed description of his proposed research program and make a brief statement of his future plans and ambitions. The candidate should select a preceptor who will follow his career throughout the period of appointment. The preceptor may be any person approved by the Deans Committee, within or without the Veterans Administra-

tion. The sponsoring hospital will describe the research and other facilities available for use by the Investigator. Additional information and assistance in completing the application should be secured from the Deans Committee or hospital manager. In making the final selection the Central Advisory Committee will consider not only the qualifications of the candidate, but the ability of the hospital to provide an atmosphere conducive to his development.

Time of awards. Selection will be made semiannually for January and July appointment. Applications may be obtained from the manager of the Veterans Administration hospital of choice. The completed forms are submitted by the Deans Committee to the Office of the Assistant Chief Medical Director for Research and Education, Veterans Administration, Washington 25, D. C. The candidates will be notified of their selection by the Chief Medical Director through the hospital manager and an announcement of the appointment will be made to the Deans Committee at the same time.

BOOKS RECEIVED

Receipt of the following books for review is hereby acknowledged. We are glad to publish complete listings of all new books received but such listing must be regarded as a sufficient return for the courtesy of the sender. Books of particular interest will be reviewed in full as time and space permit. Additional information in regard to all listed books will be gladly furnished upon request.

BONE STRUCTURE AND METABOLISM—Ciba Foundation Symposium. *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., B.Ch. and *Cecelia M. O'Connor*, B.Sc., Editors. Cloth. $8.00. Pp. 299. Little, Brown and Company, Boston, 1956.

PAPER ELECTROPHORESIS—Ciba Foundation Symposium. *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., B.Ch. and *Elaine C. P. Millar*, A.H.-W.C., A.R.I.C., Editors. Cloth. $6.75. Pp. 224. Little, Brown and Company, Boston, 1956.

THE HAPPY LIFE OF A DOCTOR. By *Roger I. Lee*, M.D. Cloth. $4.00. Pp. 278. Little, Brown and Company, Boston, 1956.

REHABILITATION LITERATURE 1950–1955. Compiled by *Earl C. Graham*, Librarian, and *Marjorie M. Mullen*, Assistant Librarian, National Society for Crippled Children and Adults. $13.00. Pp. 621. The Blakiston Division, McGraw-Hill book Company, Inc., New York, 1956.

REHABILITATION MONOGRAPH VI. SELF-HELP DEVICES FOR THE ARTHRITIC. By *Edward W. Lowman*, M.D., The Institute of Physical Medicine & Rehabilitation, New York University-Bellevue Medical Center, New York. Paper. $1.00. Pp. 123. The Institute of Physical Medicine & Rehabilitation, New York University-Bellevue Medical Center, 400 East 34 Street, New York 16, N. Y.

LIVING WITH A DISABILITY. By *Howard A. Rusk*, M.D., Director, Institute of Physical Medicine and Rehabilitation, and *Eugene J. Taylor*, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York. Cloth. $4.00. Pp. 207. The Blakiston Company, Inc., Garden City, New York, 1953.

HISTAMINE—Ciba Foundation Symposium jointly with The Physiological Society and The British Pharmacological Society. *G. E. W. Wolstenholme*, O.B.E., M.A., M.B., B.Ch. and *Cecelia M. O'Connor*, B.Sc., Editors. Cloth. $9.00. Pp. 472. Little, Brown and Company, Boston, 1956.

THE PATHOLOGY AND SURGERY OF THE VEINS OF THE LOWER LIMB. By *Harold Dodd*, Ch.M. (Liverpool), F.R.C.S. (Eng.), Surgeon to St. Mary's Hospital (London) Group, and Royal London Homeopathic Hospital, Ilford and Royal Hospital, Richmond, and *Frank B. Crockett*, M.S. (Lond.), F.R.C.S. (Eng.), Surgeon to St. Thomas's Hospital, London, with a foreword by *R. R. Linton*, M.D., Assistant Clinical Professor of Surgery, Harvard Medical School, Visiting Surgeon and Chief of the Peripheral Vascular Clinic, Massachusetts General Hospital, Boston, Massachusetts. Cloth. $12.50. Pp. 462. E. & S. Livingstone Ltd., Edinburgh and London, 1956. Agents in United States: The Williams & Wilkins Company, Baltimore, Maryland.

Books for review should be sent to *Edward Henderson, M. D., Editor-in-Chief*, 236 Midland Avenue, Montclair, New Jersey.